AN INVESTIGATION INTO THE MIGRATION OF FENESTRATED AORTIC STENT-GRAFTS

UNIVERSITY OF LIVERPOOL

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

By

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JULY 2013

DECLARATION

I declare that the work presented in this thesis, which was conducted in part at the Regional Vascular Unit, Royal Liverpool and Broadgreen University Hospitals, and at the School of Health Sciences, University of Liverpool, is my own, and has not been accepted in any previous application for a degree. All sources of information have been specifically acknowledged. This thesis is submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Philosophy.

31st July 2013

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DEDICATION

For

Anna, Alicia and Evangeline, with love.

ACKNOWLEDGEMENTS

First and foremost, I wish to acknowledge my supervisors Dr Marta García-Fiñana and Professor Richard McWilliams for their tireless and unwavering support from the very outset. It is with no doubt, that without the support, encouragement and constructive advice received this PhD would not have materialised.

I am also grateful to Dr Diane Scutt who gave me the initial courage to embark on a PhD. I am also indebted to Dr Scutt for her early support and guidance as my initial primary supervisor and research mentor. Dr Scutt has now retired for the University and I would like to wish her every happiness with this new chapter of her life.

My special appreciation goes to the National Institute for Health Research (NIHR) for funding this research. I wish also to thank the British Society for Endovascular Therapy (BSET) for supporting and encouraging clinicians to participate in this study.

Data collection would have been impossible without the support of many people from the nine UK vascular centres. Particular thanks to Matt Bown, Rob Morgan, Ferdinand Serracino-Inglott, John Hardman, John Rose, Ralph Jackson, Jonathan Boyle, Steve Butterfield, Andy Platts and others who all helped facilitate the multisite data collection.

I am particularly grateful to Femi Oshin, Rana Canavati and Steve Jones, who as vascular research fellows, proved instrumental in overcoming the challenges of bureaucracy within the National Health Service.

Finally, where would I be without the support of my wonderful wife? Three years of study with absences for courses and to present at conferences. Thank you.

ABSTRACT

An investigation into the migration of fenestrated aortic stent-grafts

Andrew England

Rupture of an abdominal aortic aneurysm (AAA) is usually lethal. Fenestrated stent-grafts provide a valuable treatment option for patients with complex AAA. However, complications from this treatment have been reported. One possibility is that the device moves (migrates) under the force of pulsatile blood, leading to reperfusion of the AAA, with the possibility of rupture or occlusion of a side-branch with disastrous consequences. Within the literature, there is an absence of information regarding the migration of fenestrated aortic stent-grafts. In addition, there are no validated techniques available for assessing migration. This thesis describes work with the following aims: (i) to validate a computed tomography (CT) central luminal line (CLL) technique for quantifying stent-graft migration. (ii) to report the incidence, timings and related sequelae for proximal and distal migration of the Zenith fenestrated AAA stent-graft (iii) to investigate the predictive factors for proximal migration of a fenestrated stent-graft.

Results from the validation experiment (where 2 mm MDCT scans were used) showed that it is possible to detect stent-graft migration ≥ 4 mm. The CT CLL technique was piloted on a single centre cohort of 55 patients treated with a Zenith fenestrated AAA stent-graft. The 1st postoperative CT scan was considered as the baseline. Stent-graft position (proximal and distal) was then compared against all subsequent CT scans. Survival analysis, using interval censored data, estimated that 9% (95% CI 0% to 17%) and 22% (95% CI 7% to 34%) of patients will experience proximal migration at 12 and 36 months, respectively. Distal iliac limb migrations were less frequent, 5% (95% CI 0% to 11%) and 15% (95% CI 3% to 24%) at 12 and 36 months, respectively. Data from a larger multicentre cohort (154 patients, 9 UK centres) were also analysed. Proximal migrations were all caudal in direction (median +6.0, IQR +4.5 to +7.9 mm), distal migrations were cranial (median -6.1, IQR -7.8 to -5.1 mm). For proximal migration, at 12 and 36 months, rates were 18% (95% CI 11% to 25%) and 23% (95%CI 15% to 30%), respectively. Distally, iliac migration was seen in 15% (95% CI 8% to 21% and 35% (95% CI 20% to 48%) of patients, at 12 and 36 months, respectively. Analysis of survival curves identified no differences in proximal migration rates in patients with and without complications (P=0.84), or who required reintervention (P=0.81).

Multivariate analysis, using a Cox proportional hazards model, identified 1st postoperative CT neck length as a consistent risk factor for proximal migration (Hazard ratio 0.90, 95% CI 0.78 to 0.97, $P<0.05$). A 10% reduction in proximal migration hazard exists for every mm increase in aortic neck length. Follow-up aortic diameter changes at the caudal renal artery, contralateral iliac limb diameter and changes in the SMA to cranial renal artery length during follow-up were identified as risk factors based on certain assumptions of event times. An absence of preoperative CT scans for some patients did place some limitations on the overall risk factor analysis.

This research has introduced new literature on the quantification, incidence, related-sequelae and risk factors for fenestrated stent-graft migration. Overall, the results from this thesis estimate that migration occurs in around a third of patients by four years, but is not associated with an increase in sequelae. Future research should investigate migration in new devices and help devise more robust methods for capturing multicentre imaging data and tracking patients lost to follow-up.

CONTENTS

LIST OF PUBLICATIONS

The following publications arose as a direct result of this PhD thesis.

England, A., McWilliams, RG. Migration and dislocation of aortic devices during follow-up. In: Branchereau, A., Jacobs, M., ed 2008. Endovascular Aortic Repair: The State of the Art. Turin, Edizioni Minerva Medica.

Oshin OA, England A, McWilliams RG, Brennan JA, Fisher RK, Vallabhaeni SR. (2010). Intra- and interobserver variability of target vessel measurement for fenestrated endovascular aneurysm repair. *J Endovasc Ther* **17**(3):402-7.

England, A., García-Fiñana M, How TV, Vallabhaneni SR, McWilliams RG. (2011). The accuracy of computed tomography central luminal line measurements in quantifying stent graft migration. *J Vasc Surg* **55**(4):895-905.

England A, Murphy M, McWilliams RG. Endovascular Aortic Aneurysm Repair. In: Cowling, M., ed 2012. Vascular Interventional Radiology: Current Evidence in Endovascular Surgery. London, Springer-Verlag.

England A, McWilliams R. (2013). Endovascular Aortic Aneurysm Repair (EVAR). *Ulster Med J* **82**(1):3-10.

England A, García-Fiñana M, Fisher RK, Naik JB, Vallabhaneni SR, Brennan JA, McWilliams RG. (2013). Migration of fenestrated aortic stent grafts. *J Vasc Surg* **57**(6):1543-52.

LIST OF PRESENTATIONS

The following conference presentations were delivered as a direct result of this PhD thesis.

England A, García-Fiñana M, Scutt ND, Vallabhaneni SR, McWilliams RG. 2011. 'The accuracy of CT Central Luminal Line (CLL) measurements in quantifying stent-graft migration'. Presented at the British Society for Endovascular Therapy Annual Meeting, BSET, Warwick, UK.

England A, García-Fiñana M, Vallabhaneni SR, Fisher RK, Naik JB, Brennan JA, McWilliams RG. 2011. 'Migration of fenestrated aortic stent-grafts: assessment using thin-slice CT'. Presented at the British Society for Interventional Annual Meeting, BSIR, Glasgow, UK. **Best abstract prize.**

England A, García-Fiñana M, Vallabhaneni SR, Fisher RK, Naik JB, Brennan JA, McWilliams RG. 2012. 'CT acquisition parameters and their effects on the quantification of stent graft migration'. Paper presented at the British Society for Endovascular Therapy Annual Meeting, BSET, Warwick, UK.

England A, García-Fiñana M, Vallabhaneni SR, Fisher RK, Naik JB, Brennan JA, McWilliams RG. 2013. 'An investigation into fenestrated stent-graft migration using follow-up CT scans '. Presented at the International Symposium on Endovascular Therapy Annual Meetin, ISET, Miami, US.

England A, García-Fiñana M, Vallabhaneni SR, Fisher RK, Naik JB, Brennan JA, McWilliams RG. 2013. 'Migration of fenestrated aortic stent-grafts: assessment using thin-slice CT'. Presented at the Multidisciplinary European Endovascular Therapy Congress, MEET, Rome, Italy.

England A, García-Fiñana M, McWilliams RG & BSET Collaborators. 2013. A multicentre investigation into migration of the Zenith fenestrated aortic stent-graft. Paper presented at the British Society for Endovascular Therapy Annual Meeting, BSET, Warwick, UK. **Best abstract prize**.

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ABBREVIATIONS

AAA	Abdominal Aortic Aneurysm
AUI	Aorto-uni-iliac
ASA	American Society of Anesthesiologists
BSET	British Society for Endovascular Therapy
CA	Coeliac axis
CIA	Common iliac artery
CFL	Central Flow Line
CLL	Central Luminal Line
CT	Computed Tomography
CTA	Computed Tomography Angiography
DICOM	Digital Imaging and Communications in Medicine
DREAM	Dutch Randomized Endovascular Aneurysm Management
ECG	Electrocardiogram
ENGAGE	European Stent Graft Natural Selection Global Postmarket Registry
EVAR	Endovascular Aneurysm Repair
EUROSTAR	EUROpean collaborators on Stent-graft Techniques
FDA	Food and Drugs Administration
FEVAR	Fenestrated Endovascular Aneurysm Repair
HU	Hounsfield unit
IC	Interval censoring
ICVS	Institute for Cardiovascular and Venous Surgery
IFU	Instructions for Use
IIA	Internal iliac artery
IQR	Inter-quartile range
KM	Kaplan Meier

LRA	Left renal artery
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MDCT	Multi-Detector Computed Tomography
MPR	Multi-planar reformatted projections
NHS	National Health Service
OSR	Open Surgical Repair
PACS	Picture Archiving and Communications System
RCT	Randomised controlled trial
RLUH	Royal Liverpool University Hospital
RRA	Right renal artery
SD	Standard deviation
SE	Standard error
SMA	Superior Mesenteric Artery
SVS	Society of Vascular Surgery
UK	United Kingdom
UKSAT	UK Small Aneurysm Trial
US	United States
2D	Two-dimensional
3D	Three-dimensional

1. Rationale and summary of investigations

An abdominal aortic aneurysm (AAA) is a permanent localised dilatation of the abdominal aorta (Metcalfe *et al.*, 2011). For those aged between 65 and 80 years the incidence of an AAA is 7.6% in men (Ashton *et al.*, 2002) and 4.2% in women (Singh *et al.*, 2001). If left untreated, Wilmink and Quick estimate that a third of these aneurysms will eventually rupture (Wilmink and Quick, 1998). Rupture of an AAA is usually lethal with overall mortality rates of up 90% common (Bengtsson and Bergqvist, 1993). Historically, management of an AAA was based on elective open surgical repair (OSR), replacing the aneurysmal segment with a vascular prosthetic graft. OSR has now largely been superseded by the deployment of a covered stent (stent-graft) delivered by minimal surgical access through the common femoral arteries. Stent-graft repair, or more precisely endovascular aortic aneurysm repair (EVAR) is now the most common method for the elective management of an AAA (Jackson *et al.*, 2012). Potential advantages of EVAR over OSR include a reduced time under general anaesthesia, elimination of pain and trauma associated with major abdominal surgery, reductions in total hospital stay and in the intensive care unit, and reductions in blood loss (National Institute for Health and Care Excellence, 2009).

EVAR involves the internal lining of the diseased segment of aorta using a stent-graft. The stent-graft comprises a metallic (stainless steel or nitinol) skeleton covered with an impermeable (polytetrafluoroethylene or polyester) fabric and is implanted using fluoroscopic guidance. The goal of the procedure is to divert blood away from the weakened aortic wall and this is achieved by the stent-graft sealing in the aortic wall above the

aneurysm and in the common iliac arteries below. This results in the exclusion the aneurysm from systemic circulation and the prevention of a potentially fatal rupture.

The major randomised controlled trials (RCTs) which have compared EVAR with OSR have consistently demonstrated lower mortality rates favouring EVAR (based on the first 30-days following repair). In the UK EVAR 1 trial 30-day mortality was 1.7% for EVAR versus 4.7% for OSR (Greenhalgh *et al.*, 2004). The Dutch DREAM trial produced similar results, 30-day mortality rates were 1.2% for EVAR versus 4.6% for OSR (Blankensteijn *et al.*,2005). The more recent US OVER trial showed lower 30-day mortality rates for both EVAR (0.5%) and OSR (3.0%) (Lederle *et al.*, 2009). The improved results in both arms of the OVER trial may be attributable to the inclusion of smaller AAA (43% had a maximum diameter <5.5 cm), differences in pre, intra- and post-operative care and the restriction to using only Food and Drug Administration (FDA) approved stent-grafts. EVAR is not without its limitations, complications such as endoleak, renal impairment, device migration, aneurysm growth and rupture are occurring at a higher rate than anticipated (Clagett, 2008). Large RCTs have also documented a 20-30% higher complication rate for EVAR when compared to OSR (United Kingdom EVAR Trial Investigators, 2010; De Bruin *et al.*, 2010). A further limitation of EVAR is that it is only feasible in patients who satisfy certain anatomical requirements. It has been suggested that around 50% patients are not candidates for standard EVAR (Ricotta and Oderich, 2008). These patients would normally have required more complex OSR which is associated with increased mortality and morbidity from cardiopulmonary and renal complications (Svensson *et al.*, 1993, Cambria *et al.*, 2002, Sarac *et al.*, 2002).

The extension of the fabric component of the stent-graft above the level of the renal arteries has further allowed the expansion of EVAR into more complex AAAs. This treatment

was first described by Park and colleagues in 1996 (Park *et al.*,). Initial reports of this technology, fenestrated endovascular aneurysm repair (FEVAR), have demonstrated that it can be successfully and safely performed (Anderson *et al.*, 2001, McWilliams *et al.*, 2004). To date more than 3,000 fenestrated stent-grafts have been implanted worldwide and feasibility is now no longer an issue (Amiot *et al.*, 2010). Internationally, the bulk of the FEVAR experience rests with the Zenith fenestrated AAA endograft (Cook Medical Inc, Bloomington, IN). Over the past few years several other manufacturers have developed fenestrated devices and these also provide a treatment option for complex AAA (Bungay *et al.*, 2011, Holden *et al.*, 2013).

All stent-grafts, including fenestrated, are subjected to downwards displacement forces from pulsatile blood leaving the heart. These downward displacement forces act longitudinally and challenge the fixation of the stent-graft. Failure of fixation will lead to migration of the device with the possibility of late type I or III endoleaks and associated risk of aortic rupture (Harris *et al.*, 2000; Wyss *et al.*, 2010). Additional problems may also result and include stent-graft distortion and kinking, which may in turn lead to a secondary thrombosis. For fenestrated stent-grafts, migration could be even more catastrophic. Fenestrated stent-grafts typically incorporate the origins of the renal and visceral arteries within the fabric component of the device. Caudal migration of a fenestrated stent-graft migration could, therefore, result in the graft fabric shuttering down over the visceral artery ostia and causing a visceral artery occlusion.

For standard (infrarenal) stent-grafts the reported incidence of stent-graft migration ranges from 0 to 21% (England and McWilliams, 2008). Cases of fenestrated stent-graft migration have also been reported within the literature (O'Neill *et al.*, 2006a; Ziegler *et al.*,

2007; Scurr *et al.*, 2008a; Verhoeven *et al.*, 2010; Greenberg *et al.*, 2009a; Triosi *et al.*, 2011). However, within these FEVAR series, follow-up durations were heterogeneous, migration assessment methods were poorly defined and rates were commonly based on cases resulting in associated complications or requiring reintervention. Such approaches are likely to be inadequate; Greenberg and colleagues argued that subtle stent-graft migration must be detected early, preferably before complications arise (Greenberg *et al.*, 2004b). Virtually all aortic stent-grafts are based on a bifurcated design with an ipsilateral and contralateral iliac limb deployed in the respective common iliac artery. Migration of an iliac limb is also a possibility. Back in 2001, Beebe and colleagues reported on cases of iliac limb migration (Beebe *et al.*,). Migration at the distal landing zones can also result in complications, these include endoleak and thrombosis. The report by Beebe *et al.*, is one of the few reports documenting cases of migration of a distal iliac limb and reflects the need for more research in this area.

With the possibility of post-EVAR complications it is mandatory that all patients are entered into a planned surveillance programme. For fenestrated stent-grafts this usually consists of multi-detector computed tomography (MDCT) scans at 1-month, 6-months and annually thereafter. From these serial MDCT scans it is possible to track the position of the aortic stent-graft, at both the proximal and distal landing zones, over time.

There are concerns within the vascular community that migration of a fenestrated stent-graft could be potentially disastrous. There is an absence of data on the incidence, timings and related sequelae for fenestrated stent-graft migration. Understanding the causal factors for migration is also important. Identification of risk factors could guide patient selection, identify the need for modifications to stent-graft design and direct follow-up

strategies. These points are particularly important since the clinical and cost-effectiveness of FEVAR is a huge issue for both funding bodies and regulatory agencies.

There is clearly an absence of literature investigating migration of fenestrated aortic stent-grafts. Cases of migration can significantly impact on the patient and can also increase the total cost of the procedure. The aim of this thesis was to undertake an investigation into the migration of fenestrated aortic stent-grafts. In doing so, this thesis reports the incidence, timings and related complications and reinterventions of fenestrated stent-graft migration. Additional analyses were also conducted in order to establish any risk factors for the migration of fenestrated aortic stent-grafts.

THESIS OUTLINE:-

Chapter 2: ***Abdominal aortic aneurysms, endovascular repair, outcomes and complications.*** This chapter provides an in-depth review of the literature underpinning this thesis. Areas of research that this thesis focuses on are described in detail.

Chapter 3: ***Aortic displacement forces and stent-graft migration.*** This chapter introduces the physiology of aortic displacement forces and provides a more detailed outline of stent-graft migration, including its assessment and the fixation mechanisms for an aortic stent-graft.

Chapter 4: ***Study into the accuracy of CT central luminal line measurements in the quantification of stent-graft migration.*** This chapter uses a combination of aortic phantoms and clinical CT data to experimentally assess the validity of using a CT CLL measurement technique for the quantification of stent-graft migration. Data from this experiment is used

in subsequent chapters to provide a definition of stent-graft migration and confirm the validity and reliability of the assessment technique.

Chapter 5: ***Study into the single centre experience of fenestrated stent-graft migration.*** This was a pilot study investigating the incidence, timings and related sequelae for proximal and distal (iliac) migration of a Zenith fenestrated AAA stent-graft at a single UK institution.

Chapter 6: ***Study into the multicentre experience of fenestrated stent-graft migration.*** This study expanded on the previous single centre work and reports fenestrated stent-graft migration data from a series of large UK vascular centres. Incidence, timings and related sequelae for both proximal and distal (iliac) migration were again reported.

Chapter 7: ***Study into the predictive and protective factors for proximal migration of a Zenith fenestrated AAA stent-graft.*** Based on the incidence and timings of fenestrated stent-graft migration described in the previous chapter; this study sought to identify any predictive or protective factors. Consideration was also given to whether any potentially predictive or protective factors identified had clinical significance.

Chapter 8: Discussion and future recommendations. An overview of the main findings from this thesis are presented here. There is also a full discussion of the advantages and disadvantages of the methodological approaches used. Suggestions for future research are made and finally, the contributions of thesis to the body of knowledge are given, together with an overall conclusion.

2. Introduction

2.1 Abdominal aortic aneurysms (AAA)

An abdominal aortic aneurysm (AAA) is a permanent dilatation of the abdominal aortic ≥ 3 cm in diameter (Metcalfe *et al.*, 2011). The incidence of AAA varies on the basis of age and gender; reports suggest that 1.7% of women and 5% of men have an aortic diameter ≥ 3 cm by the age of 65 years (Scott *et al.*, 1991). The prevalence of an AAA then increases by 6% per additional decade of life thereafter (Greenhalgh and Powell, 2008). Male gender, smoking, hypertension, hyperlipidaemia, chronic obstruction pulmonary disease (COPD) and family history are all strong risk factors for the development of AAA (Vardulaki *et al.*, 2000, Brady *et al.*, 2004).

The pathogenesis of AAA formation is complex and not yet fully understood. Atherosclerotic plaques are a feature of an AAA and there is some belief that AAA formation is a consequence of advanced atherosclerosis (Nordon *et al.*, 2009). Commonly the natural history of atherosclerotic arterial disease is progressive arterial stenosis eventually leading to occlusion. If atherosclerosis is the initiating event in AAA pathogenesis then it is unclear why some individuals progress to an occlusive state and others to aneurysmal disease (Baxter and Worth, 2008). Other theories include a systemic dilating diathesis which is primarily governed by genotype (Kuivaniemi and Elmore, 2012) or the option that changes in the abdominal aorta may be a demonstration of a diseased vascular tree resulting from a chronic inflammatory process (Jagadesham *et al.*, 2008). Although the pathophysiology remains unclear it is likely to be due to a genetic predisposition (Bown *et al.*, 2011) combined with environmental factors contributing to the formation of aneurysms in anatomically vulnerable

vessels (Nordon *et al.*, 2009). AAA are typically characterised by the destruction of elastin and collagen in the aortic wall, loss of media smooth muscle cells with thinning of the vessel wall and transmural infiltration of lymphocytes and macrophages. The result is a permanent localised dilatation of all three vessel layers of abdominal aorta and if left untreated, disease progression may lead to aneurysm rupture and death.

For the majority of patients AAA are asymptomatic and are detected incidentally. Clinical symptoms usually arise from complications relating to the arterial aneurysm – namely rupture, thrombosis, or distal embolisation (Thompson and Bell, 2000). For many symptomatic patients the first clinical manifestation is rupture (Brown *et al.*, 1999). Autopsy and clinical studies have suggested that the risk of rupture accelerates with increasing aortic diameter (Darling, 1970, Glimaker *et al.*, 1991). For AAA less than 5.5 cm in diameter the risk of rupture is generally low, above this threshold the risk increases markedly (Greenhalgh and Powell, 2008). In a population-based study by Nevitt and colleagues no ruptures were reported during a 5 year follow-up for AAA <5 cm, but a 5% annual rupture risk was demonstrated for AAA >5 cm in diameter at initial presentation (Nevitt *et al.*, 1989). Data from the UK Small Aneurysm Trial (UKSAT) calculated the annual rupture risk for AAA <4 cm at 0.3%. This rose to 1.5% for 4.0-4.9 cm AAA and 6.5% for 5.0-5.9 cm AAA (Brown and Powell, 1999). There is almost universal agreement that the rupture risk is very low for AAA <5 cm in diameter and that the risk increases substantially after 6 cm. Variation does exist within the literature regarding the estimation rupture risk for specific AAA diameters (Brewster *et al.*, 2003) (Table 2.1). Such differences may reflect differences in the number of females (Brown and Powell, 1999), mean blood pressures (Cronenwett *et al.*, 1985) and the

smoking status (MacSweeney *et al.*, 1994) of individuals included in the different comparator studies.

Table 2.1 Estimated annual rupture risk. Source: Brewster et al., 2003

AAA diameter (cm)	*Rupture risk (%/yr)*
<4	0
4-5	0.5-5
5-6	3-15
6-7	10-20
7-8	20-40
>8	30-50

In England and Wales ruptured AAA accounts for approximately 7,000 deaths per year (Office for National Statistics, 2012). These are similar numbers as for gastric, oesophageal and prostatic malignancies (Office for National Statistics, 2000). Rupture is usually lethal and overall mortality rates of up to 90% have been reported (Bengtsson and Bergqvist, 1993). The management of AAA places a large burden on healthcare resources, in England it accounts for over 11,000 hospital admissions per year (Thompson and Bell, 2000). Interestingly, unlike other atherosclerotic vascular disorders, the incidence of AAA appears to be rising (Acosta *et al.*, 2006). Reasons for this are unknown. Norman and Powell (2007)

have suggested that since AAA formation appears to be a late event following smoking exposure, these trends may reflect temporal changes in smoking prevalence (Norman and Powell, 2007). Rupture of an AAA is now the 13th commonest cause of death in the Western world (Choke *et al.*, 2005).

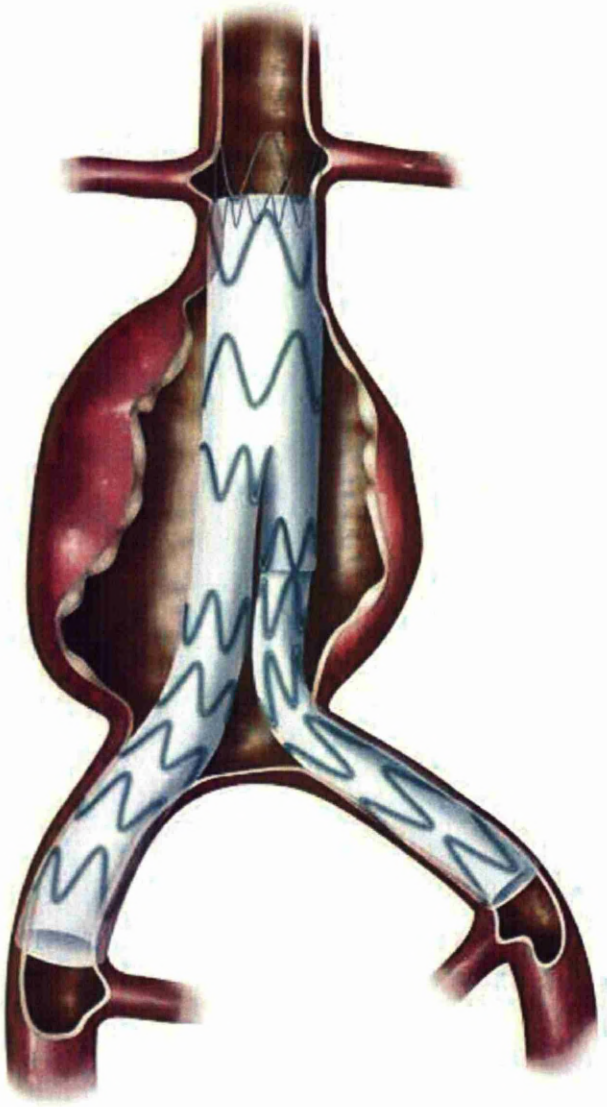
The first treatment of an AAA by open surgical repair (OSR) was undertaken in Paris by Charles Dubost in 1951 (Cervantes, 2003). This approach has remained the mainstay of AAA repair for over forty years. OSR involves the open surgical exposure of the abdominal aorta, aortic and iliac clamping followed by replacement of the diseased aortic segment using a prosthetic graft. Reports from two large RCTs, the Dutch DREAM and UK EVAR trials reported 30-day mortality rates for OSR of between 4.6% - 4.7% (Prinssen *et al.*, 2004, Greenhalgh, 2004). A report by Conrad and colleagues stated that for OSR actuarial survival was 71% and 44% and 5 and 10 years post procedure, respectively (Conrad *et al.*, 2007). However, in the same report Conrad and colleagues identified a limited number of anastomotic pseudoaneurysms, graft occlusion and infections which occurred infrequently during follow-up. Procedure-related reinterventions after OSR are also required in approximately 10.5% of patients (Kieffer et al., 2012). Despite this OSR is considered to be a predominantly durable and effective procedure. The decision to operate on a patient with an asymptomatic AAA is based on the analysis of the risk of rupture compared to the possible mortality from the elective surgical repair (Thompson and Bell, 2000). OSR in the majority of instances requires intensive or critical care nursing and the use of a general anaesthetic. There are also reports of significant levels of post-operative pain following OSR (Greenhalgh and Powell, 2008). As a result some patients are considered to be less suitable candidates for OSR. This is mainly due to the presence of coexisting medical conditions which place the

patient at a heightened risk. Two large registries have investigated OSR outcomes in high-risk patients (Bush *et al.*, 2007, Sicard *et al.*, 2006). The study by Bush and colleagues identified 1580 high-risk patients who underwent OSR. All patients were aged >60 years, had American Society of Anesthesiologists (ASA) physical grading classifications 3 or 4 and a range of co-morbidities (history of cardiac, respiratory, or hepatic disease; cardiac revascularisation, renal insufficiency, or low serum albumin level). Early (within the first 30-days of the procedure) and 1-year mortality rates were 5.2% and 12.4%, respectively. Such long-standing high mortality rates amongst high-risk patients have generated demand for the development of minimally invasive techniques (Wahlgren and Malmstedt, 2008).

2.2 Endovascular repair and aortic stent-grafts

Endovascular aortic aneurysm repair (EVAR) was developed as an alternative to OSR in order to reduce the risks from open surgery and to provide a treatment option for patients who would be otherwise unfit. The EVAR technique uses an endoprosthesis (stent-graft), which is delivered through small holes in the femoral arteries and seeks to exclude the aneurysm from the circulation by internally lining the aorta (Thompson and Bell, 2000). The stent-graft is a tube composed of a fabric suspended on a metallic mesh called a stent (Figure 2.1).

Figure 2.1 Anatomical diagram illustrating a deployed stent-graft within the infrarenal aorta. Source: (www.medtronic.com)



The stent helps to ensure rapid and stable expansion when the device is deployed within the aorta. According to Thompson and Bell (2000) there are several distinct advantages of stent-graft repair over conventional OSR (Table 2.2).

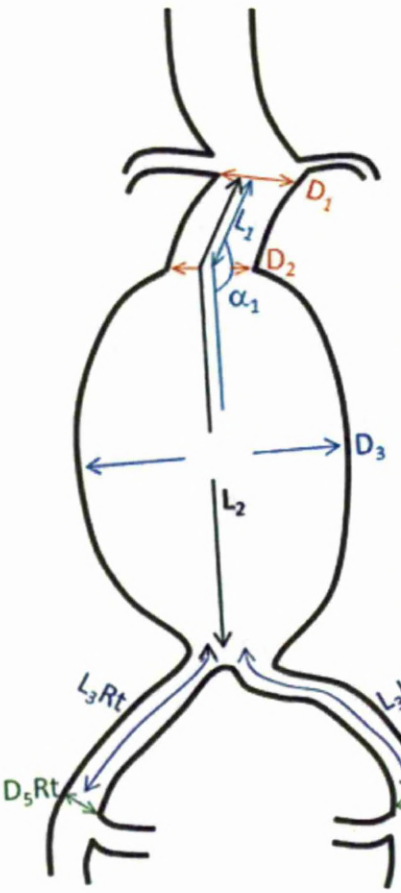
Table 2.2 Potential advantages of endovascular repair over conventional OSR. Source : (Thompson and Bell, 2000)

- No need for abdominal incision
- Avoidance of aortic cross clamping
- No retroperitoneal dissection
- Improved perioperative cardiorespiratory function
- Reduction in metabolic stress response to aortic aneurysm repair
- Improved renal and gastrointestinal function
- Reduced hospital stay

The EVAR procedure varies somewhat, depending on the specific device used. Commonly the stent-graft is an inverted Y-shape, with a main trunk for the proximal aorta and two branches for the iliac arteries. The iliac components are given the term ipsi- and contralateral depending on the deployment side of the main proximal component. Devices are generally modular and usually composed of two or three components which interconnect and are assembled within the patient. The main component is inserted through the ipsilateral common femoral artery and is advanced into the infrarenal abdominal aorta. The proximal end of the endograft is deployed immediately below the most caudal renal artery. The distal ends of the graft are then deployed within their respective common iliac arteries.

EVAR is only feasible in patients who satisfy certain specific anatomical requirements (Figure 2.2). It has been estimated that around 50% of patients with AAA are not candidates for conventional EVAR because of unfavourable anatomy (Ricotta and Oderich, 2008). These include patients with short or angulated necks or complex aneurismal involvement of the juxtarenal, paravisceral, and thoracoabdominal aorta.

Figure 2.2 Criteria typically used to assess anatomical suitability for EVAR for three commonly implanted stent-grafts



Manufacturers anatomical suitability guidelines for EVAR			
Parameters	**Zenith**	**Excluder**	**Endurant**
Neck angle (α_1), °	≥120	≥120	≥120
Neck diameter (D_1), mm	18-28	19-29	19-32
Neck length (L_1), mm	≥15	≥15	≥10
CIA diameter (D_5), mm	7.5-20	8-18.5	8-25
CIA length (L_3), mm	≥10	≥10	≥15
Femoral artery diameter, mm	≥8	≥8	≥8

Devices described in the above illustration are the Cook Zenith AAA endograft, Gore C3 Excluder device and the Medtronic Endurant stent-graft.

Two series have suggested that as many as 54% of patients with AAA, or as few as 14%, met the routinely used anatomical criteria for conventional EVAR (Cotroneo *et al.*, 2006, Elkouri *et al.*, 2004). Such differences can be attributed to variations in patient selection criteria between manufacturers, treatment thresholds of individual centres and improvements to preoperative and intraoperative imaging. Patients who are not eligible for standard EVAR often require complex OSR which is associated with increased mortality and morbidity from cardiopulmonary and renal complications (Svensson *et al.*, 1993, Cambria *et al.*, 2002, Sarac *et al.*, 2002). These increased rates are believed to be due to the need for higher aortic cross clamping resulting from an inadequate infrarenal aortic neck and the potential need for reimplantation of vital aortic side branches. Good surgical candidates may tolerate complex OSR but patients with large aneurysms and poor cardiac, pulmonary or renal performance have limited options (Ricotta and Oderich, 2008).

2.3 Modes of device failure

Despite lower 30-day mortality rates for EVAR when compared with open surgery (UK EVAR trial, EVAR 1.7% vs OSR 4.7%; Dutch DREAM trial, EVAR 1.2% vs OSR 4.6%)(Greenhalgh *et al.*, 2004, Blankensteijn *et al.*, 2005) and its popularity amongst the vascular community, EVAR is not without its limitations. Complications such as infection, renal impairment, device migration, endoleak, aneurysm growth, and rupture are occurring at a higher rate than anticipated (Clagett, 2008). EVAR is substantially different from OSR in that the aneurysm remains within the abdomen but is excluded from the systemic blood flow leaving the heart.

A fall in estimated glomerular filtration rate (eGFR) can often be seen following EVAR but usually reverts back to preoperative levels. Permanent damage to renal parenchyma may result from deliberate or unintentional coverage of a renal artery by the stent-graft

fabric, toxic effects of the iodinated contrast media and cholesterol emboli (Pisimisis *et al.*, 2013). The risk of acute renal impairment is lower for EVAR patients than those undergoing OSR, however, the overall renal function at 1-year is comparable (Greenberg *et al.*, 2004a).

Occlusion of a stent-graft can result from poor blood flow due to either graft kinking or a poor outflow (Cochennec *et al.*, 2007). The incidence within the literature varies between 2 and 40% depending on the stent-graft type and the length of follow-up (Maldonado *et al.*, 2004, Carroccio *et al.*, 2002, Erzurum *et al.*, 2004, Laheij *et al.*, 2000, Ouriel *et al.*, 2003). Graft thrombectomy and adjunctive stenting may be undertaken to correct any related symptoms. If a stent-graft limb is lost through occlusion then, for some patients, a femoro-femoral crossover graft may be necessary.

Infection of an aortic stent-graft is rare and single-centre case series estimate an incidence of between 0.5 to 1.3% (Ducasse *et al.*, 2004, Sharif *et al.*, 2007, Heyer *et al.*, 2009). Bacterial contamination of the stent-graft can occur during implantation, in the periprocedural hospitalisation or later due to an aortoenteric fistula (Veger *et al.*, 2013). If infection is present then treatment with appropriate antibiotic therapy is recommended and management should be similar to that for an infected surgical graft (Sharif *et al.*, 2007).

Vascular access for EVAR is typically performed with bilateral femoral cut-down arteriotomies. Serious groin access complications are rare but can include haematoma, infection and seroma with a reported incidence of between 1 and 10% (Liaw *et al.*, 2009). Occasionally a groin will need to be re-explored in order to repair a false aneurysm or evacuate a haematoma. Very rarely patients who have undergone EVAR may suffer embolisation of the lower limb from arterial debris dislodged during the stent-graft

implantation (Greenhalgh *et al.*, 2004). Treatment is generally difficult and care must be taken when manipulating the device within the aorta especially for cases where there is severe mural thrombus within the aortic neck. If distal embolisation does occur then treatment will be predominantly guided by the level of underlying ischaemia.

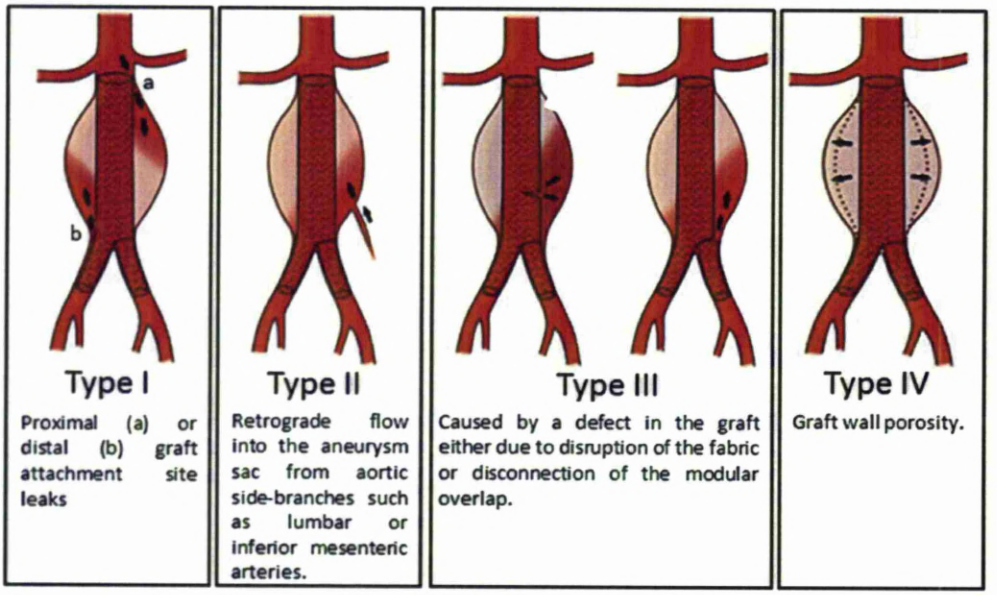
Systemic Inflammatory Response Syndrome (SIRS) or post-implantation syndrome can occur within a few days of the EVAR procedure and is seen in around 35% of patients (Arnaoutoglou *et al.*, 2011). Signs and symptoms generally include fever, leucocytosis and raised inflammatory markers.

Wireform fractures have been reported for most stent-grafts (Jacobs *et al.*, 2003). These fractures may lead to diminished stent strength and loss of radial force which can result in migration. Additionally the jagged ends of fractured metal may cause tears in the fabric and subsequent endoleaks. Stent factures are best demonstrated on plain abdominal radiographs. The use of serial plain radiographs during follow-up is well established. Migration, metallic fractures and conformational changes can all be detected using a combination of AP and lateral abdominal radiographs (Verhoeven *et al.*, 2011). The diagnostic accuracy of this examination is improved by adherence to specific plain radiography protocols (such as the LIVERPOOL/PERTH post-EVAR radiography protocol) (Murphy et al., 2003).

An endoleak is defined as blood flow within the aneurysm sac but outside of the stent-graft and can be either graft-related or non-related (White et al., 1998, White et al., 1997). Endoleaks are relatively common and several classification systems have been

proposed for describing endoleaks (White et al., 1997, White et al., 1998, Veith et al., 2002) (Figure 2.3).

Figure 2.3 Illustration of endoleaks using the classification system devised by White and May. Adapted from Veith et al., 2003



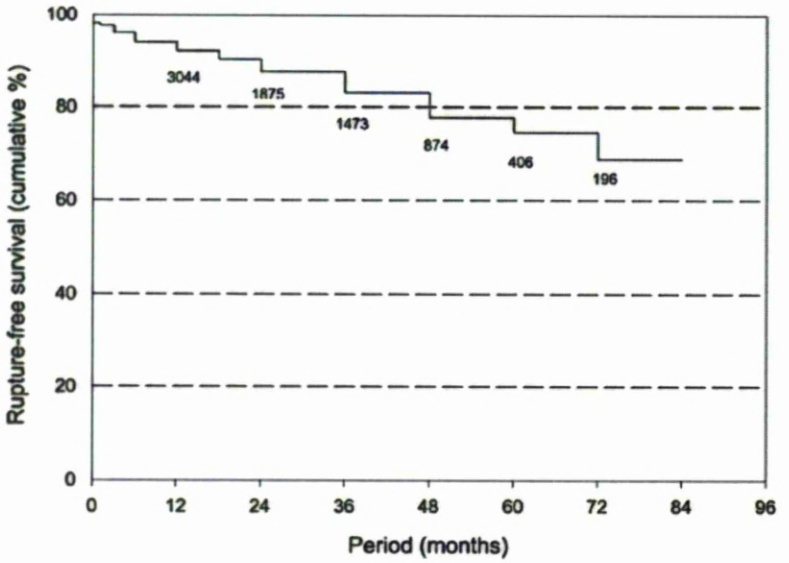
Amongst 2463 patients in the EUROSTAR registry, 171 (6.9%) had an endoleak on their 1-month follow-up, and 317 (12.9%) patients developed one during the remaining follow-up period (mean 15.4 months) (van Marrewijk *et al.*, 2002). More recent data from the UK EVAR 1 trial reported the presence of endoleaks in 118 (22.2%) patients (UK EVAR Trial Participants, 2005). These included 27 type I, 79 type II, 8 type III and 4 unspecified endoleaks. The most serious endoleaks are types I and III which are associated with aneurysm enlargement and rupture. Secondary intervention to correct these endoleaks is almost always necessary. Rupture in the presence of a type II endoleak has also been reported within the literature (Jones *et al.*, 2007), however, these are generally considered to

have a more benign course and a conservative management approach is usually adopted unless there is evidence of continuing aneurysm sac enlargement (Bashir *et al.*, 2009).

Stent-grafts are subjected to distraction forces due to the relentless force of pulsatile blood flow. These distraction forces act longitudinally and challenge the fixation of the graft and the overlap zones. The stent-graft resists these forces due to its fixation mechanisms which include radial force of the sealing stent and the barbs which engage into the aortic wall. The columnar strength of a device is also important in resisting distraction. Distraction forces are dependent on a patient's blood pressure and the cross-sectional area reduction between the proximal/aortic and distal/iliac sealing stents (Sutalo *et al.*, 2005). Failure of fixation will lead to migration or modular disconnection with late type I or type III endoleak and the risk of aortic rupture. Graft limb distortion with subsequent thrombosis can also arise secondary to device migration.

Failure of the stent-graft may lead to the aneurysm becoming exposed to pulsatile blood and, therefore, exposing the patient to the risk of potentially lethal rupture. In one of the largest registry series published the EUROSTAR collaborators reported rupture-free survival rates following EVAR (Figure 2.4) and noted that post-EVAR rupture was associated with a 60% mortality (Fransen *et al.*, 2003b).

Figure 2.4 Life table of rupture-free survival in the entire EUROSTAR cohort of 4291 patients. Figures next to the curve represent number of patients at risk for each interval (Fransen et al., 2003)



The EUROSTAR registry demonstrated that migration, type 1 and 3 endoleaks, and graft kinking are predictive of graft rupture and generally these complications necessitate some form of reintervention (Harris *et al.*, 2000). A more recent publication by Schlösser and colleagues in 2009 reported on 270 cases of post-EVAR rupture (Schlosser *et al.*, 2009). In this series the cause of rupture was identified in 218 (81%) out of 270 cases. Endoleaks accounted for 160 cases (59%), graft migration 41 (15%), graft disconnection 11 (4%) and infection 6 (2%). This work also identified that the majority of post-EVAR ruptures occurred within years 2 and 3 following repair, however, this report was based on a review of 110 journal articles and the overall follow-up was not specified.

2.4 Follow-up imaging surveillance

In view of the distinct possibility of complications during follow-up it is mandatory that all patients are entered into a planned graft surveillance programme. Evidence suggests that post-EVAR rupture is more likely in patients with a previously reported complication or

signs of failed EVAR (Wyss *et al.*, 2010). The EUROSTAR registry reported on outcomes of 2846 patients who had EVAR between 1999 and 2004. Reintervention rates at 1, 2, 3 and 4 years in this registry were 6%, 9%, 12% and 14%, respectively (Hobo and Buth, 2006). The UK EVAR trial reported similar rates of 8%, 8%, 11% and 16%, respectively (Brown *et al.*, 2010). The incidence of complications and reinterventions appears to be greatest during the first six months following graft deployment (particularly the first 30 days post-implantation), with a lull from 6 to 24 months and then a new increase. This late increase has also been demonstrated with the EUROSTAR registry data (Hobo and Buth, 2006). Studies which have reported EVAR outcomes beyond five years have continued to report complications and secondary interventions in years 6 and 7 (Coppi *et al.*, 2008, Nordon *et al.*, 2010). Complications can, therefore, occur at any time point and often require the need to reintervene. Based on current evidence post-EVAR follow-up surveillance must be recommended for life, the exception would be patients with contraindications to secondary intervention e.g. severe comorbidities.

2.5 Extending the scope of EVAR

According to vascular surgical reporting standards, short-neck infrarenal AAA are classified as juxtarenal aneurysms if the aneurysm extends up to, but does not include the renal arteries (Chaikof *et al.*, 2002b). Suprarenal aneurysms, therefore, extend above and involve the renal arteries and possibly the splanchnic arteries (Amiot *et al.*, 2010). The classification of juxtarenal aneurysms is complicated and depending on the definition the incidence ranges from 2% to 20% for all AAA (Crawford *et al.*, 1986, Qvarfordt *et al.*, 1986, Taylor *et al.*, 1994). Regardless of the definition, all patients with a short-neck (<10 mm), juxta- or suprarenal AAA will have an insufficient amount of normal aorta (aortic neck) between the renal arteries

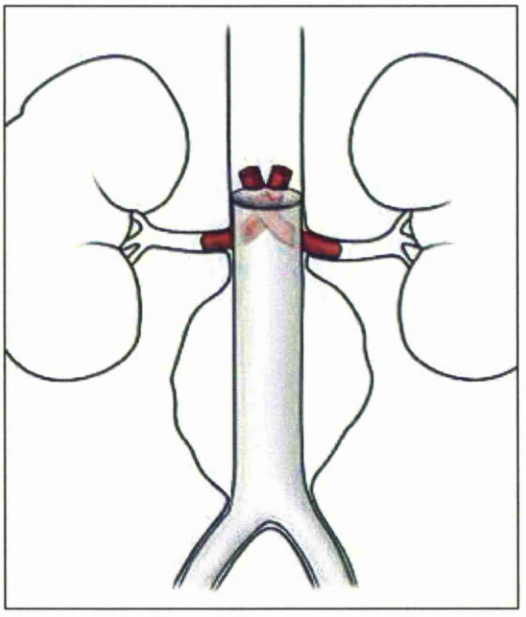
and the aneurysm sac in order to allow a standard (infrarenal) stent-graft to obtain a seal and provide protection from rupture. These patients fall into a group who are deemed to have an '*unsuitable aortic neck*'. The cut-off length is usually <10 mm between the most caudal renal artery and the start of the aneurysm (Schanzer and Messina, 2012). However, the concept of an unsuitable aortic neck has been further expanded and includes patients who have highly angulated (>60°) aortic necks and/or where there is the presence of significant thrombus/atheroma or calcification (Green, 2002, Dillavou *et al.*, 2003). This concept of an unsuitable aortic neck is a well-established term for excluding a patient from EVAR but its presence can also make OSR more challenging (Malina *et al.*, 2008).

The first reported use of an endovascular stent-graft was by Nicholas Volodos in Kharkov, Soviet Union in 1987 (Volodos *et al.*, 1988). It was the later publication by Juan Carlos Parodi and associates in 1991 (Parodi *et al.*, 1991) that was responsible for the widespread introduction of EVAR across the globe. Since these two reports substantial advances have been made in every aspect of endovascular technology. Techniques have now evolved which allow the endovascular implantation of specialised stent-grafts into the realms of complex AAA (Resch *et al.*, 2010). Several recent studies have highlighted the use of conventional stent-grafts outside of the manufacturer's *Instructions for Use (*IFU) for patients with complex AAA (Schanzer *et al.*, 2011, Igari *et al.*, 2013). Schanzer and colleagues further highlighted that post-EVAR aneurysm sac enlargement was higher in patients treated outside of the IFU and raised concerns about the long-term risk of aneurysm rupture in such patients. It is clear that for complex AAA both OSR, and EVAR outside of the IFU can generate additional problems. Even with EVAR outside of an IFU there will still be some

patients where a definitive surgical option (open or endovascular) remains unavailable. In view of this restriction further expansion of stent-graft technology has been warranted.

Chimney techniques have been proposed as an option for extending the reach of EVAR in patients with complex AAA (Moulakakis *et al.*, 2012). The chimney procedure involves the deployment of a stent-graft into aortic side-branches and the deployment of the aortic stent-graft such that the proximal parts of the visceral stents are parallel to the main aortic endoprothesis and extend above (Figure 2.5).

Figure 2.5 A standard aortic stent-graft deployed with fabric above the origin of the renal arteries. Bilateral renal artery chimney grafts are in place to maintain visceral artery perfusion. Source: www.vasculardiseasemanagement.com



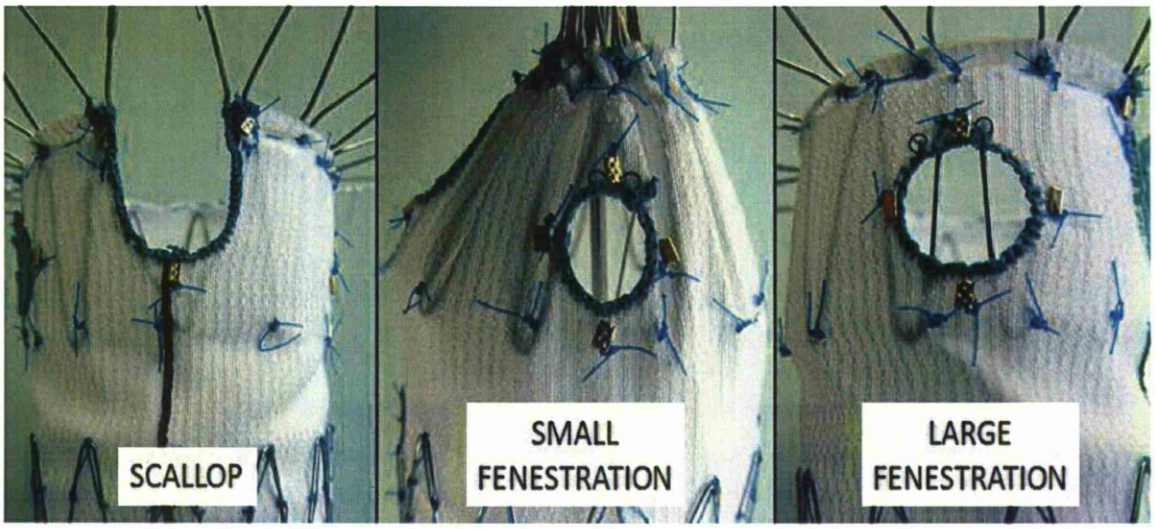
Two recent systematic reviews (Moulakakis *et al.*, 2012, Tolenaar *et al.*, 2012) included 168 patients treated using the chimney EVAR technique. These reviews reported 99% technical success rates and chimney stent-graft patency rates of ≥ 97%. Technical

success was defined as successful implantation of the stent-graft along with exclusion of the aneurysm. It should be noted that the follow-up periods for both reviews were relatively short (Moulakakis *et al.*, mean 9.0 SD 1.0 months; Tolenaar *et al.*, range 2 days to 52 months). In spite of these results there still appears to be reasonable hesitation within the vascular community to embrace this method for treating complex AAA.

2.6 Fenestrated stent-graft technology

In order to achieve a durable seal for short-necked, juxta- and supra-renal AAA the first covered portion (sealing stent) of the stent-graft must be placed over the orifices of the renal and possibly superior mesenteric and coeliac arteries. This can be achieved using a standard endovascular stent-graft when the procedure is combined with either open visceral revascularisation (Verhoeven *et al.*, 2009) or as previously described, using a chimney procedure. The chimney procedure has many opponents and there are still patients who would be considered unfit for an open revascularisation hybrid procedure. There is a further, completely endovascular procedure, available for short-necked, juxta- and supra-renal AAA and uses individually customised fenestrations within the graft fabric (Malina *et al.*, 2008). Such fenestrations allow essential blood flow to the aortic side-branches whilst allowing a seal to be achieved at or above the level of the renal arteries (Figure 2.6).

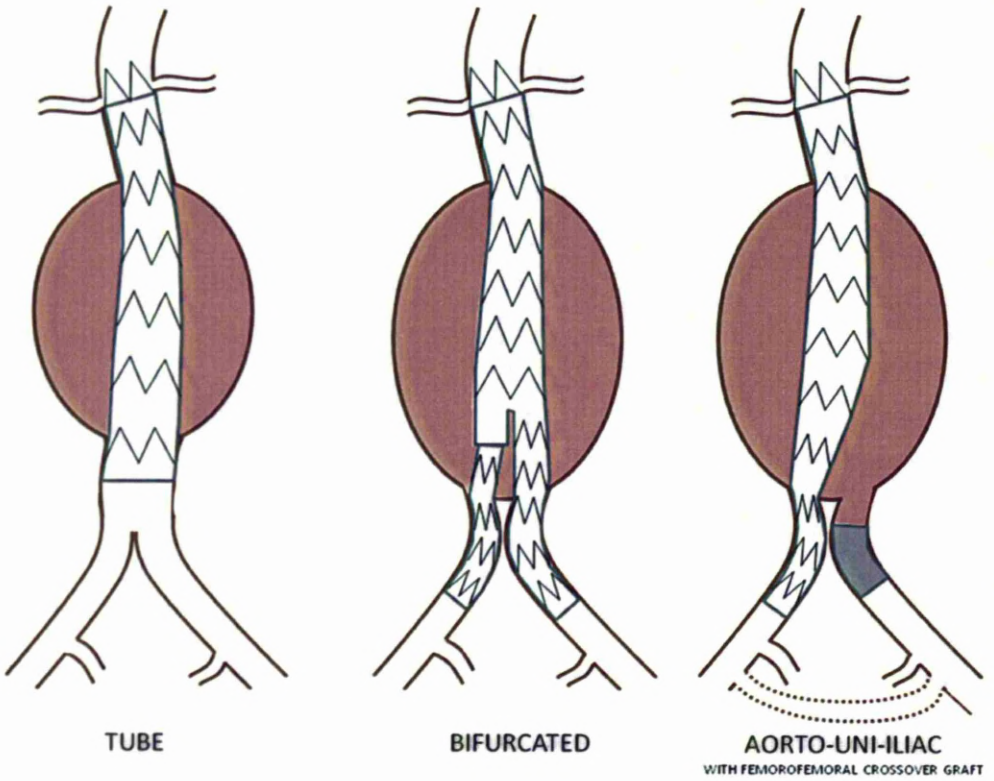
Figure 2.6 Options for preserving blood flow into aortic side-branches using a Zenith fenestrated stent-graft (Cook Medical Inc, Bloomington, IN)



Fenestrated stent-grafts are individually customised devices based on the precise plans of the location of the visceral arteries generated using pre-operative thin-slice CTA data. The fenestrations and scallops are carefully located within the graft fabric in order to match the ostia of the renal, superior mesenteric and coeliac arteries. Stent-graft deployment must, therefore, be precise and is significantly more complex than for standard infrarenal EVAR. The incorporation of the visceral arteries into the fenestrated repair does, however, generate additional (FEVAR-specific) complications (Halak *et al.*, 2006).

Historically, the only commercially available CE-marked fenestrated stent-graft was made by Cook Medical Inc (Bloomington, IN) and was based on the Zenith AAA endovascular graft. The Zenith device comprises a woven polyester fabric suspended on Gianturco stainless steel stents. The main configuration of the Zenith fenestrated stent-graft is a bifurcated stent-graft device, although aorto-uniliac and simple tube devices are available for order (Figure 2.7).

Figure 2.7 Three typical configurations of endovascular stent-graft



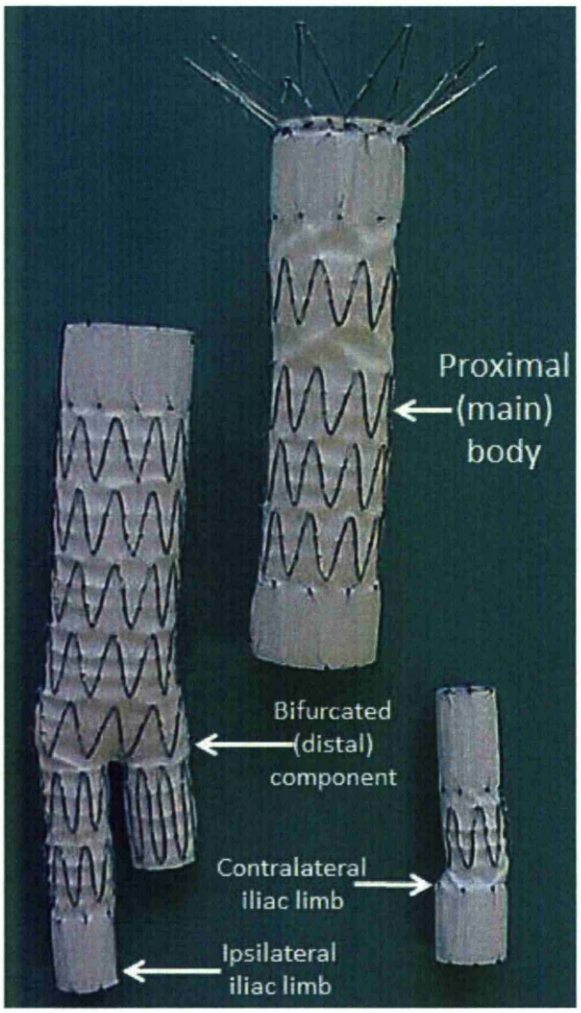
A bare metal anchor stent is available proximally which has additional barbs mounted on the bare metal in order to improve device fixation. Immediately below the bare metal anchor stent sits the fabric covered sealing stent. A device may consist of multiple fabric covered seal stents and these would include up to four customised fenestrations and provide a proximal seal whilst preserving blood flow into the visceral arteries. The device is modular with an individually customised proximal component. The distal bifurcated body has a long ipsilateral iliac limb and a short contralateral limb. The manufacturer recommends a minimum overlap with the proximal body of two stents. It is also recommended that the iliac limbs cover the entire common iliac artery segments where possible.

There are three distinct types of fenestration options available on the Zenith AAA endovascular graft (scallop, small and large fenestration) (Figure 2.6). There are manufacturing limitations to the height, width and vertical positioning of the fenestrations within the respective Gianturco stents.

A scallop describes a U-shaped gap within the proximal fabric of the stent-graft. Small and large fenestrations are generally circular and are placed below the start (proximally) of the endograft fabric. Scallops and small fenestrations typically have no metallic struts across them and, therefore, are generally stented to help maintain alignment and resist longitudinal as well as rotational migration. Large fenestrations traditionally had a stent strut crossing the opening but are now available strut free and are commonly used for securing the SMA or CA.

The extension of the fabric component of the stent-graft above the level of the renal arteries using a fenestrated stent-graft was first described in 1996 (Park *et al.*, 1996). This was then followed by the development of a more versatile fenestrated device by Lawrence-Brown, Anderson, and Hartley (Anderson *et al.*, 2001). Fenestrated stent-grafts (Figure 2.8) are designed to extend the proximal sealing zone from the infrarenal segment to the juxta- and suprarenal aorta, thereby removing the limitations of the short or absent aortic necks. Initial reports of this technology (Anderson *et al.*, 2001, McWilliams *et al.*, 2004) have demonstrated that FEVAR can be successfully and safely performed. All of these early experiences were limited to a small number of patients and more recent reports have sought to establish the mid-term efficacy of this technology (BSET and GLOBALSTAR Collaborators, 2012, Haulon *et al.*, 2010, Tambyraja *et al.*, 2011).

Figure 2.8 Components of the Zenith AAA fenestrated aortic stent-graft (Cook Medical Inc, Bloomington, IN)



To date more than 1,000 fenestrated stent-grafts have been implanted worldwide and feasibility is now no longer an issue (Scurr *et al.*, 2008a) (Table 2.3). As previously stated the bulk of fenestrated stent-graft experience has been confined to a single device, Zenith fenestrated AAA endovascular graft (Cook Medical Inc, Bloomington, IN). Over the past few years several newer devices have become available including the fenestrated Anaconda

device (Vascutek, Ichinnan, Scotland)(Bungay *et al.*, 2011) and the Ventana fenestrated stent-graft (Endologix, Irvine, CA)(Mertens *et al.*, 2012).

Long-term performance of a sutured vascular graft in open abdominal aortic aneurysm (AAA) repair depends on the durability of the anastomosis and graft material. With the introduction of stent-grafts, the anastomosis has changed, and in the process has introduced some doubts regarding the long-term durability of stent-grafts. With newer stent-grafts (fenestrated) raising the stent-graft sealing zone above the level of the renal arteries this has also introduced new modes of failure (Table 2.4).

Two of the more worrisome complications in FEVAR are stent-graft migration and target vessel loss. Migration can lead to late type 1 endoleak, aneurysm enlargement, and eventually rupture (Harris *et al.*, 2000, Tonnessen *et al.*, 2004). Stent-graft migration can be potentially evermore catastrophic for a FEVAR device where any dislodgement of a fenestration may adversely affect the blood supply to visceral aortic side branches (Malina *et al.*, 2008).

Table 2.3 Summary of current outcome data for fenestrated repair of para- and juxtarenal AAA

Author(s)	Year	Origin	Device	Patients, n	Follow-up, months	Primary technical success, %	30-day mortality, %	Overall mortality, %
Semmens *et al.*	2006	Australia	Zenith	58	16.8 ± 14.4	90.5	3.4	18
O'Neill *et al.*	2006	United States	Zenith	119	19 (0-42)	100	0.8	15
Sun *et al.**	2006	Systematic review	Zenith	317	17.7 (0-46)	NR	1.1	8.3
Ziegler *et al.*	2007	Germany	Zenith	63	14 (6-77)	87.3	1.6	23.8
Scurr *et al.*	2008	United Kingdom	Zenith	45	24 (1-48)	100	2.2	13.3
Kristmundsson *et al.*	2009	Sweden	Zenith	54	25 (12-32)	90.7	3.7	22.2
Greenberg *et al.*	2009	United States	Zenith	30	24 (1-24)	100	0	6.7
Bicknell *et al.*	2009	United Kingdom	Zenith	29	12 (9-14)	98	0	6.9
Haulon *et al.*	2010	France	Zenith	80	10 (1-38)	95	2.5	5
Amiot *et al.**	2010	France	Zenith	134	15 (2-53)	96.3	2	9
Verhoeven *et al.*	2010	The Netherlands	Zenith	100	24 (1-87)	NR	1	22
Triosi *et al.*	2011	Germany	Zenith	96	25 (1-94)	NR	1.9	20.6
Bungay *et al.*	2011	United Kingdom	Anaconda	4	1 (1-6)	100	0	0
Tambyraja *et al.*	2011	United Kingdom	Zenith	29	17 (8-21)	89.7	0	14
Metcalfe *et al.*	2012	United Kingdom	Zenith	42	11 (1-54)	91.5	7	14.3
GLOBALSTAR, BSET*	2012	UK (Registry)	Zenith	318	6	99	3.5	11
Holden *et al.*	2013	Chile/New Zealand	Ventana	15	6 (1-12)	100	0	13.3
Guo *et al.*	2013	China	Zenith	9	8 (1-14)	100	0	0

Follow-up, median (range) or mean ± SD. NR – not reported; BSET – British Society of Endovascular Therapy. Primary technical success was defined as successful implantation of the stent-graft and exclusion of the aneurysm by the end of the initial implantation procedure. 30-day mortality was defined as a death within the first 30-days following the primary implantation procedure. Studies denoted by an asterisk have either been succeeded by newer reports, with longer follow-up or have been included within other publications.

Table 2.4 Summary of complication data for fenestrated repair of para- and juxtarenal AAA

Author(s)	Year	Device	Rupture / conversion	Endoleak Primary (Secondary)	Renal failure (requiring dialysis)	Target vessel patency	Reintervention rate	Migration definition	Migration rate
Semmens *et al.*	2006	Zenith	0	6.9 (3.4)	6.9 (0.0)	90.5	24	CS	3.4
O'Neill *et al.*	2006	Zenith	0	10.0 (25.2)	25.0 (3.0)	97	NR	≥ 4mm	0.8
Sun *et al.**	2006	Zenith	NR	11.2 (9.4)	13.3	90	NR	NR	NR
Ziegler *et al.*	2007	Zenith	3.2	7.9 (11.1)	9.5 (1.6)	92.6	20.6	CS	3.2
Scurr *et al.*	2008	Zenith	0	0.0 (8.9)	13.5 (1.1)	93.6	13.3	CS	2.2
Kristmundsson *et al.*	2009	Zenith	3.7	5.6 (24.1)	5.6 (0.0)	96.3	13	CS	3.7
Greenberg *et al.*	2009	Zenith	0	0.0 (20.0)	0	100	23.3	> 10 mm	3.3
Bicknell *et al.*	2009	Zenith	6.9	0.0 (20.7)	(3.4)	97	13.8	NS	NR
Haulon *et al.*	2010	Zenith	1.3	2.5 (11.3)	11.0 (1.0)	95	10	NS	NR
Amiot *et al.**	2010	Zenith	0	12.0 (9.7)	17.0 (1.5)	96	9	NS	NR
Verhoeven *et al.*	2010	Zenith	1	2	25.0 (2.0)	93.3	9	CS	1
Triosi *et al.*	2011	Zenith	NR	NR	NR	NR	26.2	CS	23.5‡
Bungay *et al.*	2011	Anaconda	0	25	0.0 (0.0)	100	25%	NS	NR
Tambyraja *et al.*	2011	Zenith	0	(20.7)	(0.0)	93.7	38%	NS	NR
GLOBALSTAR, BSET *	2012	Zenith	NR	13.8	NR	95.3	20	CS	12
Holden *et al.*	2013	Ventana	0	20	0.0 (0.0)	100	13.3	> 10 mm	0
Guo *et al.*	2013	Zenith	0	33.3 (33.3)	11.1 (0.0)	100	0	NS	0
Metcalfe *et al.*	2012	Zenith	2.4	17.0 (7.1)	11.9 (2.4)	95	21	NS	NR

All rates are quotes as percentages. NR – not recorded; NS – not stated; CS – clinically significant. ‡ data contains both branched and fenestrated stent-grafts. Studies denoted by an asterisk have either been succeeded by newer reports, with longer follow-up or have been included within other publications.

2.7 Chapter 2 - summary

Over the past 20 years there has been an accumulation of evidence showing a reduction in 30-day mortality rates for standard EVAR when compared to OSR. Additional advantages have also been reported and include a reduction in morbidity, shorter hospital stays, less demand for ICU/HDU beds and less post-operative pain. However, standard EVAR is not amenable to all patients and there are specific anatomical limitations which can exclude certain aneurysm morphologies from this type of repair.

Techniques are now readily available which expand the applicability of endovascular repair to those patients with complex (short-necked, juxta- and suprarenal) AAA. FEVAR has now started to emerge as the dominant treatment option repair of these more complex AAA. Currently FEVAR requires carefully planned and manufactured fenestrations to be cut into a custom-made device. During deployment this device must be carefully aligned in order to position the fenestrations against the corresponding visceral side-branch ostia and thus allow the preservation of blood flow.

For standard EVAR there is a higher rate of complications arising during follow-up when compared to OSR. Several of these complications have been associated with post-treatment aneurysm rupture. It is now accepted that rupture following EVAR is more likely than in patients undergoing OSR. Treatment with a fenestrated stent-graft is also not devoid of the risk from complications. The added complexity of FEVAR, including the carefully planned fenestrations within the fabric, and increased modularity, has brought additional complications. Evidence surrounding the use of FEVAR is in its infancy. Robust methodologies must be available to allow accurate outcomes data to be presented. This is

urgently required in order to satisfy both patients and the vascular community that FEVAR is a long-term durable solution for complex AAA.

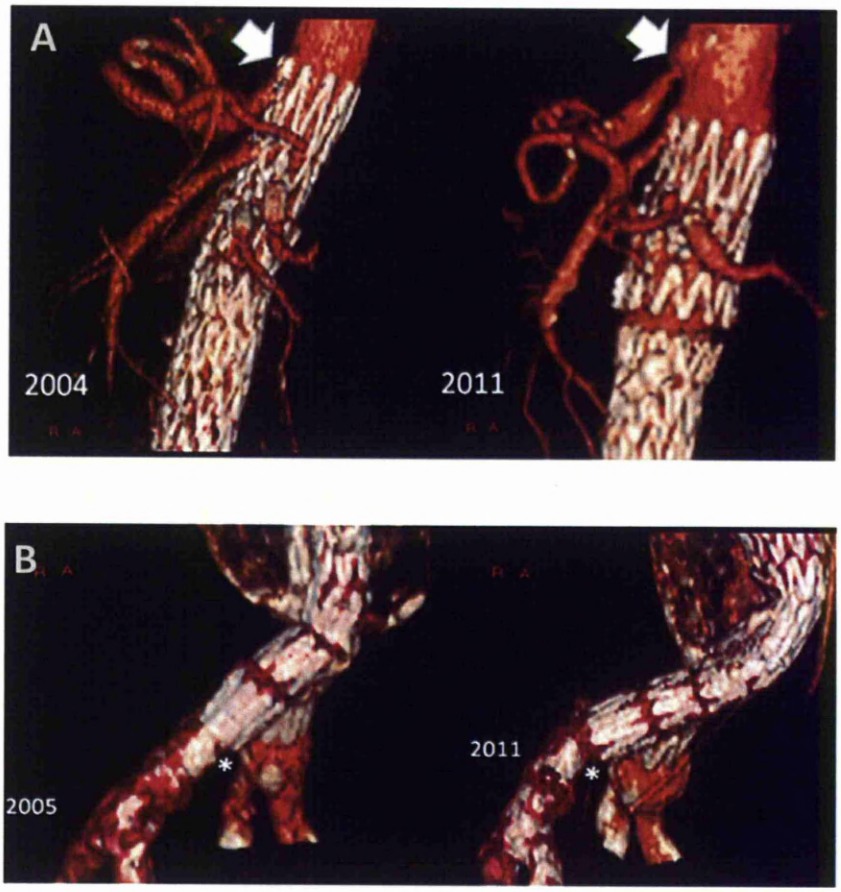
3. Device migration

3.1 Assessment

3.1.1 Definition

Device migration can simply be defined as the movement of a stent-graft from one position to another over time (Zarins, 2004). The most common scenarios involve caudal movement at the proximal attachment site or cranial movement of the iliac limb at the distal attachment site (Figure 3.1).

Figure 3.1 CT 3D volume rendered reconstructions illustrating cases of proximal (A) and distal (B) migration of a Zenith AAA fenestrated stent-graft



With increasing interest in migration there are many proposed definitions. Currently, the most widely used definition is from the reporting standards of the Society of Vascular Surgery (SVS) and the Institute of Cardiovascular and Venous Surgery (ICVS) which defines migration as ≥10 mm of stent-graft movement relative to anatomical landmarks or any migration leading to symptoms or requiring reintervention (Chaikof *et al.*, 2002b). The definition of migration is in itself complex; factors such as the imaging modality, precise assessment methodology and experience of the observer can limit the ability to identify small changes in stent-graft position. Greenberg and colleagues argues that a stricter definition of migration is needed and suggests that migration can be accurately categorised as movement of more than two times the reconstructed resolution of the imaging study (Greenberg *et al.*, 2004b). For example, in CT if using a 2mm reconstructed slice thickness then the definition of migration would be movement of ≥4 mm. Any assessment of stent-graft migration also requires that the remaining aortic neck must be taken into consideration together with the presence or absence of an endoleak. This will in turn reflect the risk of aneurysm sac pressurisation and can help guide management.

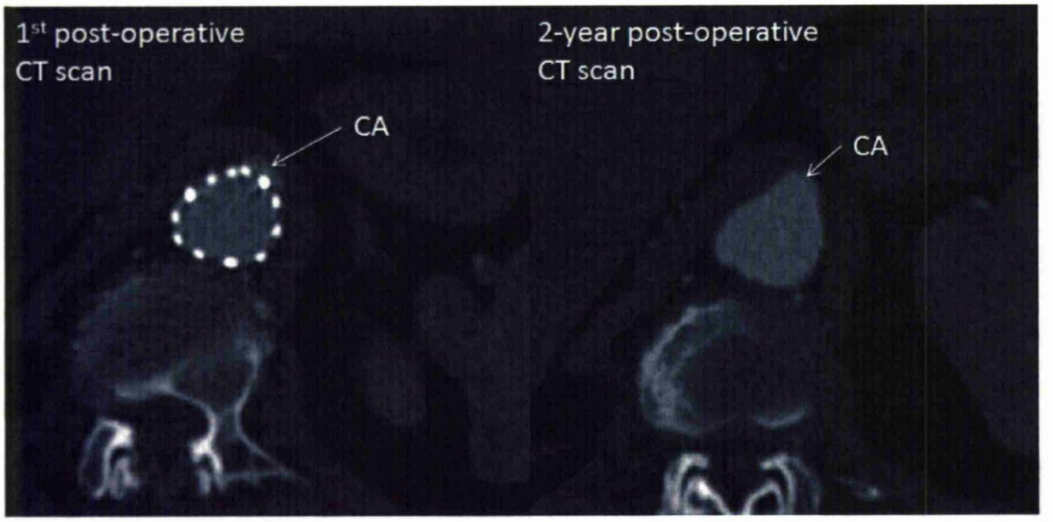
3.1.2 Identification

In the early years following the introduction of EVAR there was a major emphasis on the detection and management of endoleaks and on the assessment of changes in aortic sac morphology. Device migration has never occupied centre-stage and still many surveillance imaging examinations are not routinely scrutinised for any evidence of migration. Migration can be detected on virtually all follow-up imaging modalities (CT, abdominal radiography, MRI and ultrasound) (Uthoff *et al.*, 2012). Currently, the most common surveillance imaging examination following EVAR is MDCT angiography (van der Vliet *et al.*, 2011, Uthoff *et al.*,

2012). At many centres, MDCT angiography is considered to be the gold standard for post-EVAR follow-up (Uthoff *et al.*, 2012, Shah and Stavropoulos, 2009). Van der Vliet and colleagues in 2011 argued that MDCT angiography has the advantage of being potentially able to visualise most threats to stent-graft durability including migration, kinking, structural disintegration, endoleaks and aneurysm growth (van der Vliet *et al.*, 2011).

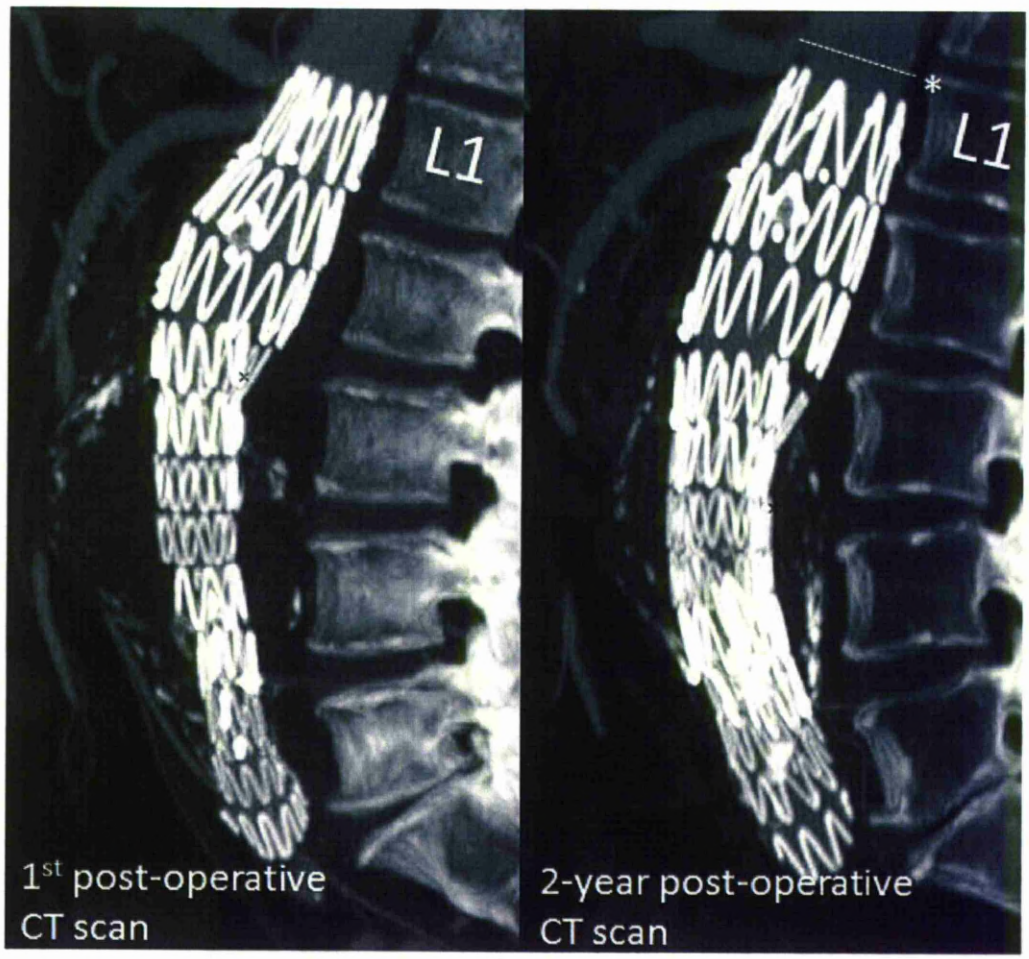
There are several post-processing image reconstruction techniques from which stent-graft migration can be detected when using serial CT examinations. In the early years of EVAR CT technology was very limited. MDCT systems were not readily available and in order to cover the required anatomy, within a single breath-hold and with sufficient arterial system enhancement, the use of thick (>5 mm) collimation was mandatory. At the same time, options for digital image review were limited. Picture Archiving and Communication Systems (PACS) were sparse and advanced computer processing techniques were still being developed. As a result the assessment of post-EVAR follow-up images almost universally relied on the evaluation of single axial CT images. From these images, migration was often identified only by the presence of an associated complication or when comparing CT images from similar table positions between follow-up examinations (Figure 3.2).

Figure 3.2 Comparison of axial CT slices (acquired in a similar position) between serial CT examinations. There is an absence of metallic struts on the 2-year CT scan suggesting the possibility of caudal migration (CA – coeliac axis)



With improvements in CT scanner technology (thinner slices and faster scanners) together with advances in computer post-processing (dedicated 3D workstations), the option of reviewing follow-up CT data as a 3D volume became available. Using these techniques the deployment position of the 1st post-operative (baseline) CT scan could be displayed using multi-planar reformatted projections (MPR). Images in the sagittal plane provided a view of the stent-graft relative to vascular branches and the lumbar vertebral bodies. When compared with similar projections from subsequent examinations (Figure 3.3) this provided the option for both subjective and objective (using electronic measurements) assessments of changes to the position of the stent-graft.

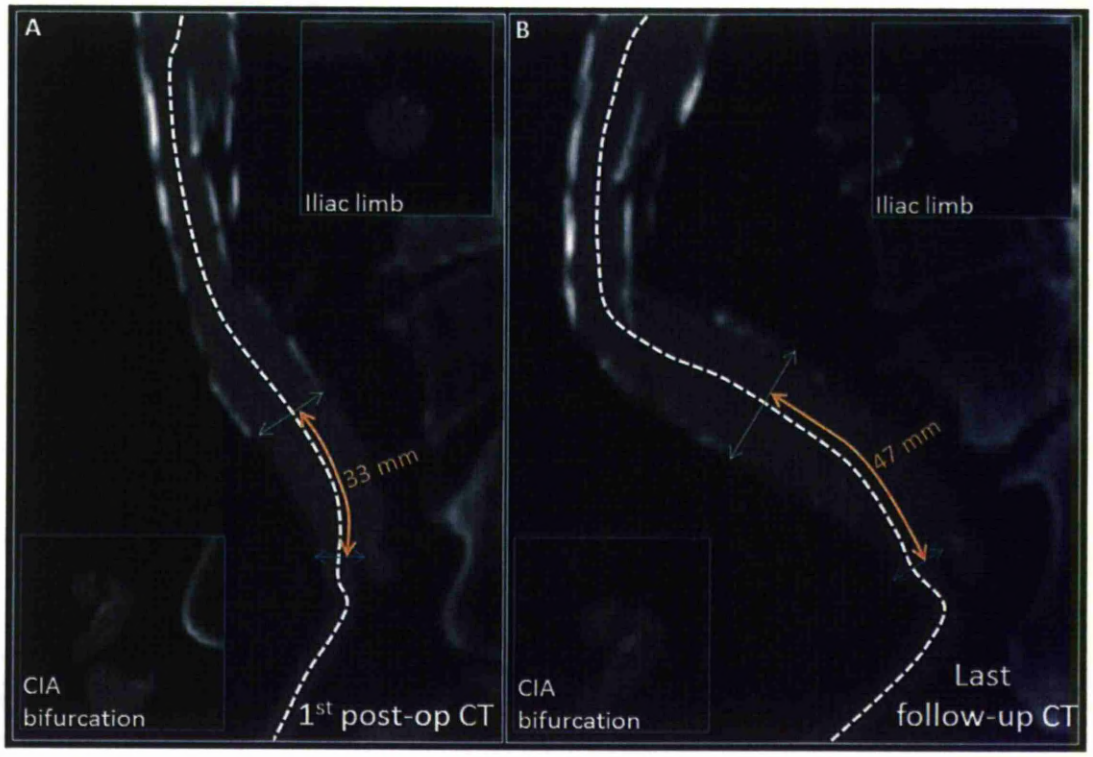
Figure 3.3 Sagittal CT reformatted MIP images from the 1st post-operative (baseline) and 2-year CT scans. There has been caudal migration of the stent-graft indicated by a difference in the position of the proximal bare stent struts (*) between the two examinations



There are, however, accepted limitations when using MPR images to provide precise length measurements along the axis of a tortuous vessel. These have been previously acknowledged within the literature (Wyers *et al.*, 2003) and as a result catheter angiography was often used to provide measurements along the length of a vessel prior to EVAR. This can also generate problems since the catheter does not always follow the central channel of the vessel and there are also well established risks from catheter angiography (Bell and Gaspar,

1982). Reports in the literature have suggested that such deviations in catheter position can cause length measurement errors. Beebe and colleagues reported that errors greater than 1 cm were present in over 19% of cases undergoing catheter angiography (Beebe *et al.*, 1995). Nowadays pre-operative catheter angiography prior to EVAR has been virtually eliminated by the combined use of MDCT with specialised 3D measurement software (Diehm *et al.*, 2004). Software algorithms on these 3D systems allow the generation of images along the centre of the contrast-enhanced lumen in the aorta and iliac arteries (Lell *et al.*, 2006). This provides a facility for precise length measurements even in the presence of tortuous or angulated anatomy (Diehm *et al.*, 2004). Such a system is likely to be superior to other techniques where measurements are based solely on a 2D projection. These central luminal line (CLL) or central flow line (CFL) measurement techniques have been validated for the preoperative assessments of vessel lengths and diameters prior to EVAR (Wyss *et al.*, 2009, Ghatwary *et al.*, 2012). No such validation data currently exists for measurements obtained from follow-up CT examinations or when assessing stent-graft migration. Stent-grafts are often deployed in tortuous or angulated anatomy and the device will typically follow the path of the vessel. Such complex anatomy is even more likely to be present if the patient is treated by FEVAR. It is, therefore, essential to have a robust migration assessment technique, such as a CLL/CFL technique, which generates accurate measurements of stent-graft position even in event of extreme vessel tortuosity or angulation (Figure 3.4).

Figure 3.4 CT central luminal line (CLL) technique used to quantify changes in the position of a stent-graft during follow-up. In this example there has been 14 mm of cranial migration of the iliac limb between the 1st post-operative (A) and last follow-up CT scan at 24 months(B)



CT surveillance following thoracic EVAR follows similar patterns to abdominal EVAR. One difference is that the assessment of migration for a thoracic stent-graft is aided by the measurement of stent-graft position using both proximal and distal aortic reference points. The proximal reference point is usually a patent aortic arch branch and the distal reference point the coeliac axis (CA). In thoracic EVAR (O'Neill *et al.*, 2006b) have demonstrated the importance of using 3D CLL technique when faced with tortuous or angulated anatomy. They reported significant advantages of using this type of technique when assessing for thoracic stent-graft migration.

Alternative imaging examinations can be used in the identification of stent-graft migration. Migration may be detected by ultrasound or be inferred by surrogate markers of possible migration. Ultrasound is not suitable for the surveillance of thoracic aneurysms but is now increasingly used as an alternative test to CT scanning in the surveillance of abdominal stent-grafts (Harrison *et al.*, 2011). Migration may be assessed with reference to a fixed aortic reference point such as the superior mesenteric artery (SMA) which is more reliably seen than the renal arteries. Migration is diagnosed if the distance from the SMA to the top of the stent-graft increases in excess of an arbitrary threshold which reflects the measurement error. Migration must also be considered when a graft-related endoleak is observed or if there is reduced limb blood flow. Graft distortion may be secondary to migration and this is the reason that altered limb blood flow must prompt a search for stent-graft migration. Ultrasound is not the optimal test for the assessment of migration and its use in surveillance is primarily to measure the sac diameter and detect endoleak. Despite this, ultrasound surveillance is typically combined with plain radiography as an alternative to MDCT.

Plain radiographs when performed to a standardised radiographic protocol such as the LIVERPOOL/PERTH protocol (Murphy *et al.*, 2003) have been suggested as being an acceptable test for migration and modular component separation. In this application migration is typically assessed by reference to non-aortic landmarks such as the vertebral bodies. It is possible that vertebral body height could change as a result of musculoskeletal degenerative processes (Allbrook, 1956). If this was to happen then cases of migration could be mimicked or cases of true migration could be masked. It would also be difficult to ascertain the proportion of aortic neck which is still covered by endograft fabric. In the

future it may be possible that implanted aortic markers, deployed as part of the initial surgical procedure, could be used to further improve the accuracy of the plain radiographic assessment of migration (Koning *et al.*, 2006).

3.2 Biomechanics of stent-graft migration

3.2.1 Displacement (drag) force

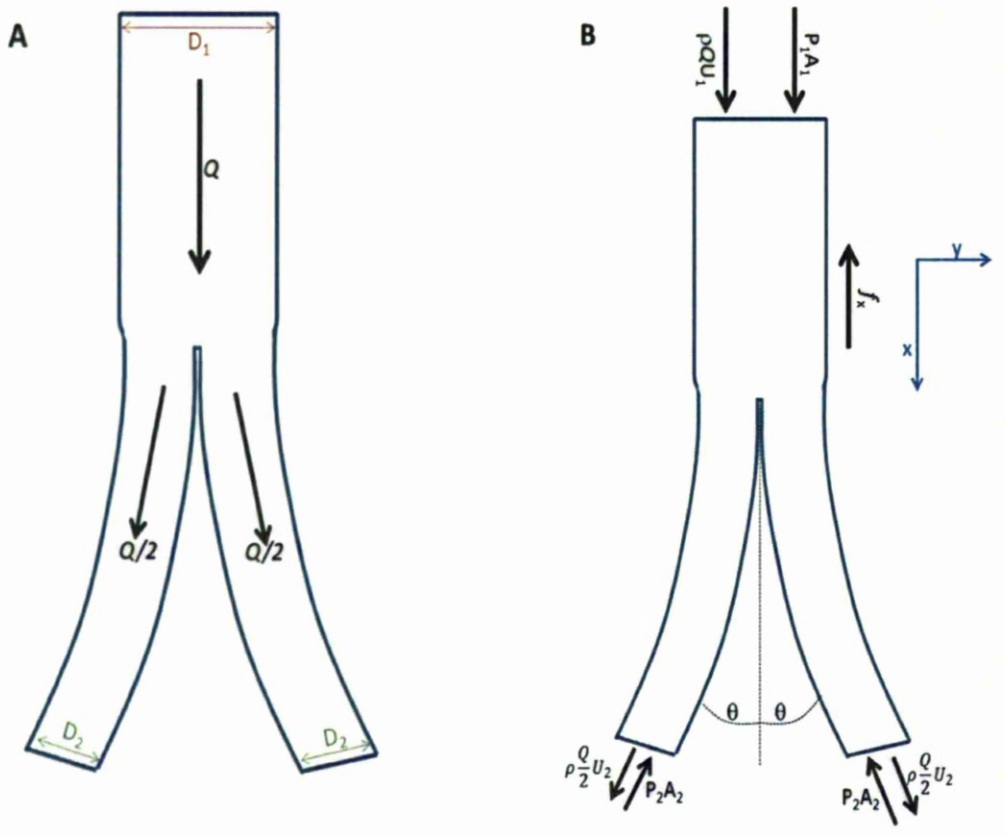
Migration can be considered as a failure of attachment within an unchanged aorta or as a failure related to changes in aneurysm morphology. Since 1998, a number of studies have attempted to determine the force required to cause the migration of an implanted aortic stent-graft using devices implanted in sections of bovine aorta (Malina *et al.*, 1998, Lambert *et al.*, 1999, Resch *et al.*, 2000, Veerapen *et al.*, 2003). The downward displacement (drag) force acting on the stent-graft includes a downward component and a transverse (or sideway) component. In general, the downward force affects the proximal neck fixation and the transverse force influences the iliac neck fixation.

The drag force on a stent-graft is not constant and will vary between patients and have some dependency on the type of stent-graft deployed. In order to explain the haemodynamic forces acting on a bifurcated stent-graft Mohan and colleagues proposed a simple model (Mohan *et al.*, 2002). In this model several assumptions were made, 1) the bifurcation is planar and symmetrical and 2) the blood flow is distributed evenly through the iliac limbs (Figure 3.5A). As the fluid enters the device it divides into two outlets of equal diameter and undergoes a change in both the direction and velocity due to the effect of the angle and the reduction in diameter. The associated change in the momentum of the fluid

and the pressure forces acting at the inlet and outlets produce forces on the device that must be opposed to prevent stent-graft migration (Figure 3.5B).

In the same report Mohan and his research group further described how the displacement forces (Figure 3.5) acting on the stent-graft can be calculated using the Massey momentum equation (Massey, 1989).

Figure 3.5 Mathematic model for studying stent-graft displacement forces (Mohan et al., 2002)



In the above figure the following terms are used D_1 = proximal cross-sectional area, D_2 = distal cross-sectional area, U_1 = proximal velocity of blood, U_2 = distal velocity of blood, A_1 = proximal cross-sectional area, P_1 = proximal pulse pressure, A_2 = distal cross-sectional area P_2 = distal pulse pressure, f_x = distal displacement force, f_y = transverse force, θ = iliac angle from vertical, Q = volume flow rate (A_1,U_1), ρ = density of the fluid.

When calculating forces it is often assumed that fluid has negligible viscosity (no fluid sheer stress and that the velocity profile is uniform) and that the bifurcation is in a horizontal plane (no gravitational forces). If this is the case then the forces acting in the axial direction (x) are summed and equated with the change in fluid momentum in the axial direction (see references included in Mohan *et al.*, 2002):

$$P_1A_1 - 2P_2A_2cos\theta - f_x = \rho Q\left(\frac{U_2}{2}cos\theta + \frac{U_2}{2}cos\theta - U_1\right) \quad (1)$$

Where P_1, A_1, U_1 and P_2, A_2, U_2 are the pressure, cross-sectional area, and velocity at the inlet and outlet, respectively. The density of the fluid is defined by ρ and Q is the volume flow rate. The first two terms on the left-hand side of Equation (1) represent the pressure forces at the inlet and outlet acting on areas A_1 and A_2, respectively. f_x is the axial component of the force exerted by the bifurcation of the fluid. The right-hand side of Equation (1) represents the rate of increase of the axial component of momentum. In the transverse direction, the pressure and momentum forces cancel out due to the assumption of symmetry and equal flow distribution and therefore f_y = 0.

Since P_2 in Equation (1) is not known, the Bernoulli and continuity equations:

$$P_1 + \frac{\rho {U_1}^2}{2} = P_2 + \frac{\rho {U_2}^2}{2} \quad (2)$$

$$A_1U_1 = 2A_2U_2 \quad (3)$$

are substituted for P_2 and U_2 in Equation (1). The volume flow rate (Q) is also substituted by A_1U_1 to obtain the following relationship for f_x:

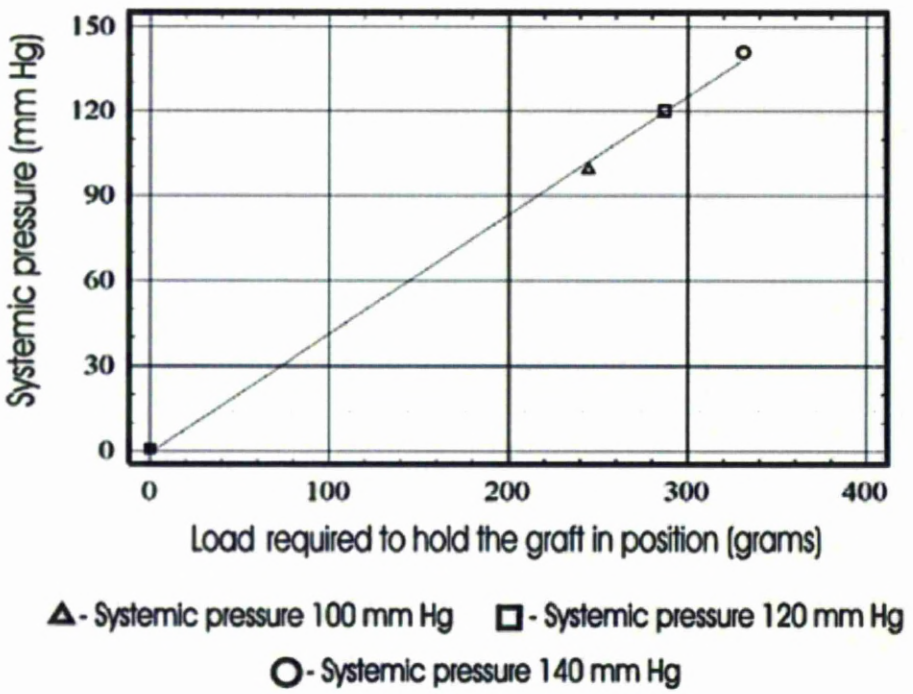
$$f_x = P_1A_1 + \rho P_1{A_1}^2 - \rho\frac{{A_1}^2}{2A_2}{U_1}^2cos\theta - 2A_2cos\theta\left[P_1 + \rho\frac{{U_1}^2}{2}\left(1 - \frac{{A_1}^2}{4{A_2}^2}\right)\right] \quad (4)$$

By Newton's third law, there is a force on the bifurcation equal in magnitude to f_x but in the opposite direction. In order to calculate the distal displacement force, blood flow rates down the infrarenal aorta and each iliac limb need to be measured or assumed. Diameters or areas of the proximal aorta and the common iliac arteries can be measured using CT imaging. The pulse pressure (pressure that is felt when feeling a pulse) can also be measured, assumed based on suggestions within the literature or varied within a displacement force model.

3.2.2 Factors affecting drag force

Using Equation (1) it can be seen that the displacement force can be affected by small changes in blood flow rate or systemic blood pressure (Q) (Volodos *et al.*, 2003) (Figure 3.6).

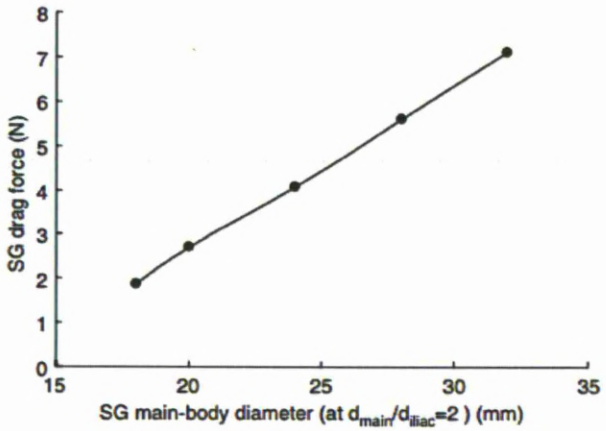
Figure 3.6 Plot of the systemic blood pressure with the means of the minimal loads required to hold a stent-graft in position assessed using an in vitro model (Source: Volodos et al., 2003)



Calculations by Li and Kleinstreuer (2006), using a fluid-structure interactions (FSI) model, concluded that blood pressure is the main contributor to drag force on a stent-graft Lambert *et al.*, in 1999 raised the question as to whether sudden rises in blood pressure may even instigate cases of migration. This latter point may be hard to prove in practice without methods for long-term ambulatory blood pressure monitoring and the simultaneous measurement of graft movement. However, hypertension has been shown to be a risk factor for migration in the EUROSTAR registry (Mohan *et al.*, 2002) and the authors again supported the conclusion that blood pressure is a major contributor to the *in vivo* distraction force.

Other variables which have an influence on the drag force upon a stent-graft include the size and shape of the aortic neck. For aortic neck diameter, the maximum drag force is only about 2N when the stent-graft diameter is 18 mm, however at 32 mm the force increases to 7 N. The almost linear dependence observed by Li and Kleinstreuer (2006) was also reported five years earlier by Liffman et al., (Liffman *et al.*, 2001). This relationship has also been illustrated graphically (Figure 3.7).

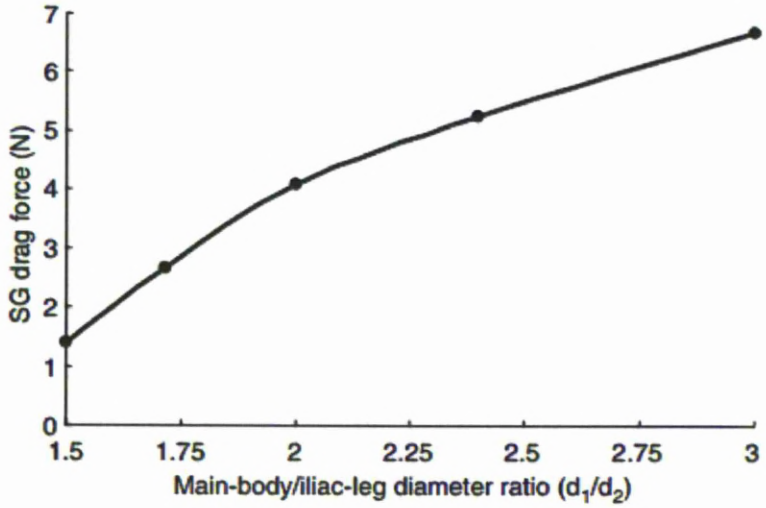
Figure 3.7 Relationship between stent-graft drag force and stent-graft size in terms of main lumen diameter (Source: Li & Kleinstreuer, 2006)



Lambert *et al.*, in 1999 conducted an *in vitro* study assessing the load needed to remove a deployed stent-graft in a series of cadaveric aortas (n=10). Their report also concluded that wider diameter aortas need less load to remove the stent-graft when compared to smaller diameter aortas (P=0.01). These findings by can be explained when considering the position of the cross-section inlet area within Massey's momentum equation (Equation 4).

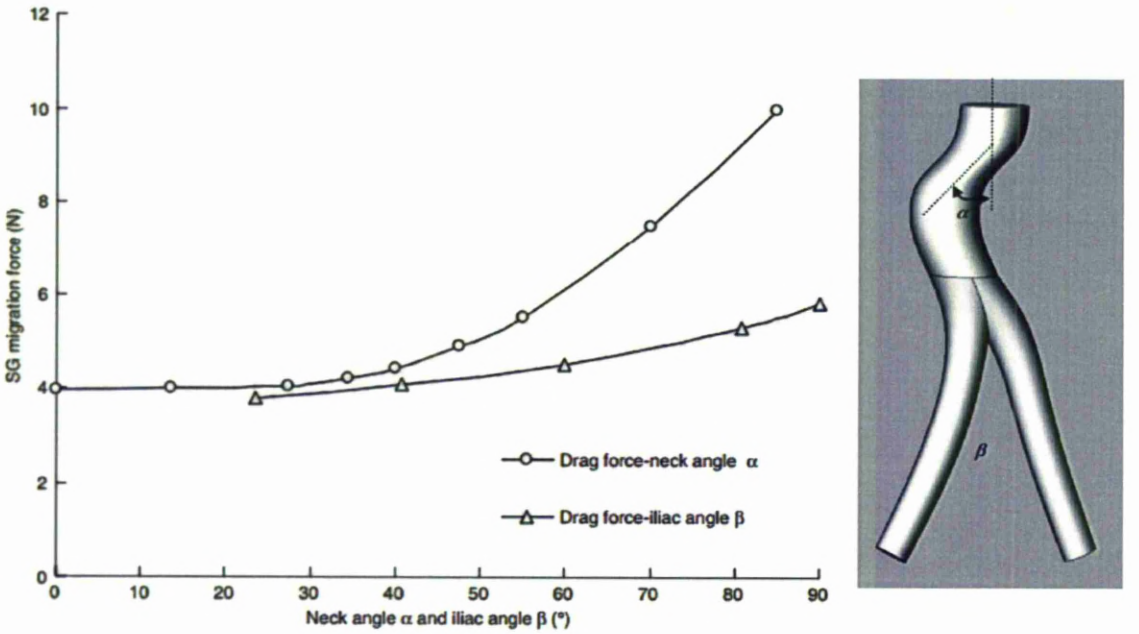
Another influential geometrical factor is the stent-graft main body to iliac limb diameter ratio. As reported by Li and Kleinstreuer (2006) using FSI a non-linear increase in drag force of around 5 N (1.5 to 6.5 N) can be observed when the ratio doubles from 1.5 to 3.0 (Figure 3.8). The reason for this is that more blood needs to converge suddenly into the smaller iliac limbs resulting in a significant net momentum change. To decrease the risk of stent-graft migration the main-body/iliac-limb diameter ratio should be as close to 1 as possible. There must be some caution when considering cross-sectional diameter measurements and the resultant displacement forces. More recent reports have utilised the cross-sectional area of a vessel, describing this as a potentially a more powerful indicator of force. This is illustrated within Massey's momentum equation where cross-sectional area is shown to have a greater influence on displacement force (Equation 4). Cross-sectional area can be determined from cross-sectional diameter, this would, however, assume that the segment being measured is perfectly circular and not-distorted. Such a situation can be difficult to achieve using radiological imaging and thus the cross-sectional diameter is often more commonly quoted. It must, however, be made clear that more precise estimations of stent-graft displacement force can be obtained when using cross-sectional area measurements.

Figure 3.8 Relationship between stent-graft drag force and main-body/iliac-leg diameter ratio (Source: Li & Kleinstreuer, 2006)



Increasing stent-graft displacement forces have been associated with increasing degrees of aortic neck angulation. Force analysis work by Li and Kleinstreuer (2006) reported that the effect of neck angle is negligible if less than 40°, however, the drag force can increase significantly if the aortic neck angle is above 40° (Li and Kleinstreuer, 2006a). Iliac angle also influences the possibility of device migration. A larger angle between the iliac limbs and main device body produces a larger drag force, the reason being that a large AAA iliac angle results in a large net momentum change. Mohan and colleagues in 2002 and more recently Morris and colleagues in 2004 demonstrated that the drag force increases in a nonlinear manner with iliac angle (Morris *et al.*, 2004). The relationship between both aortic neck (α) and iliac (β) angles and the resultant stent-graft displacement force is illustrated in Figure 3.9. In clinical studies both Albertini *et al.*, and Sternbergh *et al.*, confirmed an association between graft neck angulation and migration (Albertini *et al.*, 2000) (Sternbergh *et al.*, 2002).

Figure 3.9 Relationship between stent-graft drag force and neck angle α as well as iliac bifurcation angle β (Source: Li & Kleinstreuer, 2006)



There are other physiological parameters which affect the drag force on the stent-graft. Time variations in systemic blood pressure will affect the overall drag force during each cardiac cycle. Such time-specific variations have been described by Li and Kleinstreuer (2006) (Figure 3.10). There are variations in the blood pressure waveform between patients, this will have a resultant effect on the drag force (Li and Kleinstreuer, 2006a) (Figure 3.11). Such variations are likely to depend on the presence of any underlying cardiac and blood vessel pathologies and affect the acceleration of arterial blood leaving the heart. Supporting this Kelly and colleagues have previously described age related changes to the peripheral and carotid arterial pulse waveforms (Kelly *et al.*, 1989).

Figure 3.10 Time-variation of stent-graft drag force during the cardiac cycle (Source: Li & Kleinstreuer, 2006)

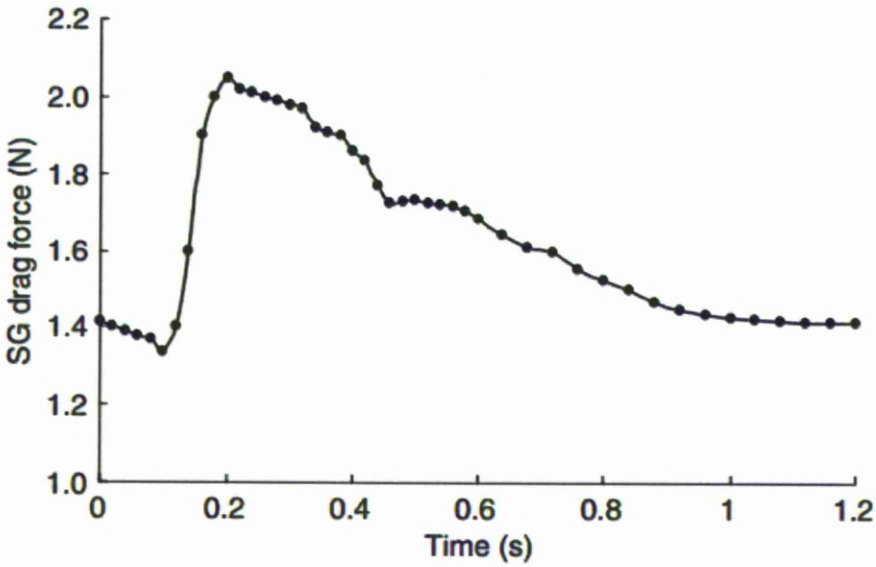
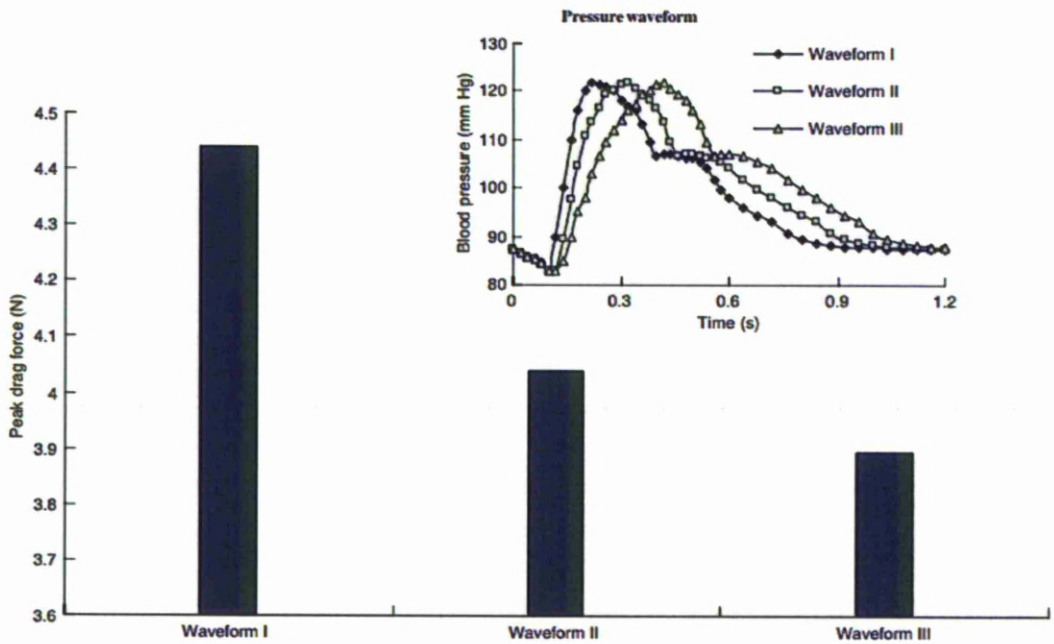


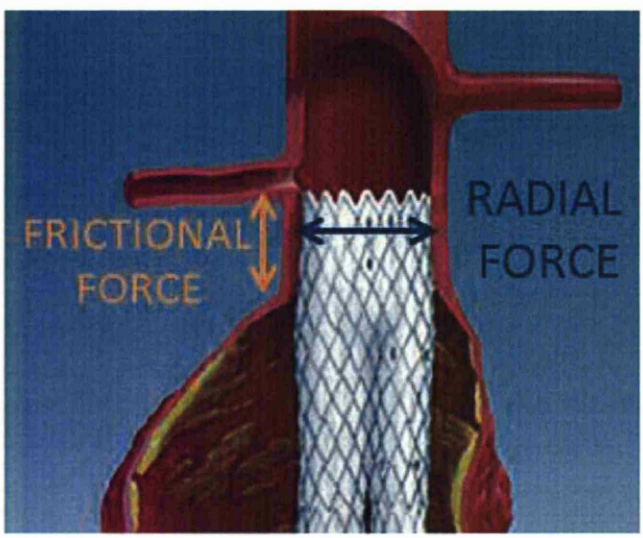
Figure 3.11 Relationship between stent-graft drag force and the type of blood pressure waveforms (Source: Li & Kleinstreuer, 2006)



3.2.3 Factors affecting fixation

In order to oppose migration and maintain positional stability within the aorta, there are contact pressure interactions between the stent-graft and the aortic wall. Experimentally, it can often be challenging to correctly capture and understand the interaction between the stent-graft and the aorta. Frictional forces are responsible for resisting the motion which may take place between the aortic wall and the stent-graft. Radial force from the stent-graft metallic skeleton and its contact with the aortic wall also resist migration (Figure 3.12).

Figure 3.12 Forces opposing proximal stent-graft migration



Many reports investigating the contact mechanics between the arterial wall and stents have assumed frictionless contacts (Bedoya *et al.*, 2006, Gijsen *et al.*, 2008, Early *et al.*, 2009, Theriault *et al.*, 2006). Friction is commonly described using the term Coefficient of Friction (CoF) which is a unitless number measuring the degree of how a surface affects the motion of objects in contact with it (Nanota *et al.*, 2003). Wu and colleagues assumed a

friction coefficient of 0.05 between a carotid stent and the artery in their computational analysis (Wu *et al.*, 2007). For aortic stent-grafts Vad *et al.*, determined a range of Coefficients of Friction (COF) for three commercially available stent-grafts (Vad *et al.*, 2010). In their report CoFs varied from 0.01 to 0.45 and were also shown to decrease with increasing oversizing. CoFs are also likely to vary with differing levels of aortic neck thrombus and calcification and as such there are likely to be differences in CoFs derived from computational techniques when compared with any *in vivo* measurements.

The radial spring force is dependent on the stent-graft construction but also the degree of oversize. Vad *et al.*, (2010) showed that by increasing the device oversize (stent-graft diameter versus native aortic diameter) this caused the contact pressure between the device and the aortic wall to increase. What was also found was that pullout forces generally increase when increasing the oversize, there is however, a plateauing point for exoskeleton nitinol based devices. In the report by Kratzberg and colleagues a plateauing point in the force needed to displace the device was seen when beyond 30% for barbed nitinol based stent-grafts (Kratzberg *et al.*, 2009). Concerns have also arisen regarding the excessive use of oversizing which may lead to gradual dilatation of the artery (Rodway *et al.*, 2008). In the US Zenith multicenter trial, stent-graft oversizing greater than 30% was the only significant predictor of migration at 12-months (Sternbergh *et al.*, 2004). For non-nitinol based devices there is an almost linear relationship between oversize and pullout force. This suggests that the radial spring force is highly important in maintaining positional stability but must be used carefully in order to prevent other complications.

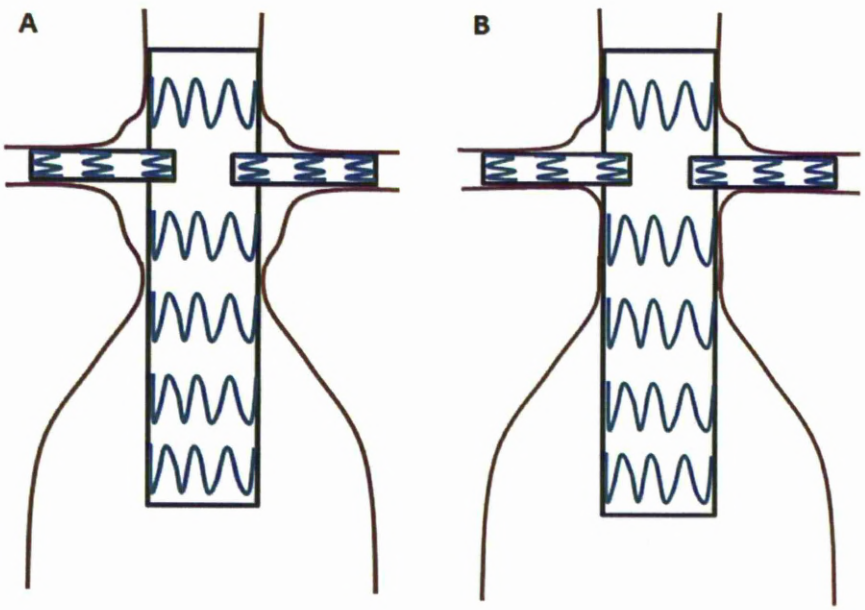
There are other factors that can affect the frictional and radial forces exhibited by the stent-graft. The constitution of the aortic wall has been shown to affect the load needed to

remove a deployed stent-graft in a series of cadaveric aortas (Lambert *et al.*, 1999). Lambert *et al.*, (1999) showed that differing calcification levels affected the loads needed to cause displacement but to a lesser effect than aortic neck length and diameters. Severe calcification of the aortic neck may restrict the barbs engaging in the aortic wall and thus reduce the frictional effectiveness of the device. Research using cadaveric aortas (Malina *et al.*, 1998) has demonstrated that by adding hooks and barbs to stent-graft devices the fixation of the device could be increased tenfold. Early clinical experience using hooks and barbs yielded relatively high migration rates, 66%, 75% and 75% at 3, 5 and 7 years, respectively (Alric *et al.*, 2003). With improvements in device technology and stent-graft implantation expertise the incidence of migration has fallen considerably. The Zenith stent-graft (with hooks and barbs) now has an accepted low migration rate, however, this has not been found to be significantly better than other stent-grafts systems which do not utilise hooks and barbs (Ouriel *et al.*, 2003, Brown *et al.*, 2007). There are also additional questions about the influence of aortic neck thrombus. The majority of clinicians are cautious about deploying a stent-graft in a thrombus lined neck in view of the likelihood of endoleak (Antoniou *et al.*, 2013). Further to this there is also some unease about the additional possibility of microembolisation (Saratzis et *al.*, 2013). As a result it would be difficult to ascertain the influence of aortic thrombus on migration using *in vivo* methods.

Shorter aortic necks have also been shown to require a smaller load in order to displace the stent-graft ($p<0.001$) (Lambert *et al.*, 1999). This relates to the contact pressure which will depend on the contact area between the aortic stent-graft and the vessel wall. As highlighted in Figure 3.13, there can also be differences in the area of aortic wall directly in contact with the device (apposition). Even in the presence of the same cardiovascular

physiology and identical devices there will be differences in the drag resistance because of differences in contact area. This feature is likely to be highly variable for fenestrated stent-grafts since there will be varying amounts of aneurysmal disease across the visceral aortic segment.

Figure 3.13 An illustration to show possible differences in aortic wall/stent-graft interface which would affect resistance to the displacement force



Even when good initial fixation has been achieved, progression of the aneurysmal process is still possible (Nasim *et al.*, 1996, Rodway *et al.*, 2008). Aortic neck dilatation has been identified as a risk factor for migration by many authors (Cao *et al.*, 2002, England *et al.*, 2004). Following EVAR up to one third of patients will experience proximal neck dilatation whilst the prevalence of device migration is much lower (Oberhuber *et al.*, 2010). It is notoriously difficult to predict patients who will experience proximal neck dilatation and subsequent migration. Late neck dilatation (>30-days following implantation) following EVAR

is a major cause of concern because of the potential loss of a proximal attachment site seal. Significant neck dilatation should be taken into consideration when outlining the surveillance programme for a particular patient, even in the absence of any adverse events. Surveillance intervals should be kept under regular review as initial neck expansion may plateau out over time (May *et al.*, 1996). A contributing factor to neck dilatation is the radial force from the stent-graft, this may vary between devices and is certainly affected by the degree of stent-graft oversizing. Experimental work has been undertaken which suggests that self-expanding stents may be superior to balloon-expandable stents in the presence of a dilating vessel (Mangell *et al.*, 1996). Opposing opinions have suggested that aortic neck dilatation results from using self-expanding stent-grafts (Dalainas *et al.*, 2007).

Studies have shown that the *net* downward displacement force on a stent-graft is significantly reduced in the presence of an endoleak (Li and Kleinstreuer, 2006b). For patients with endoleaks both sides of the stent-graft are exposed to pressure forces (Ellozy *et al.*, 2004). Even in the presence of an excluded aneurysm the will still be some pressure between the stent-graft and the aneurysm wall. Any reduction in sac pressure will not occur immediately and according to Sonesson *et al.*, this could take up to several months (Sonesson *et al.*, 2003). Hynecek and colleagues reported on the complete radiological exclusion of an AAA in 13 subjects with near complete elimination of intrasac pressure (<20%) (Hynecek *et al.*, 2007). Part of the net downward displacement force will be a function of the remaining intrasac pressure. In addition to endoleak, residual sac pressure is likely to depend on multiple factors including the presence or absence of patent side branches, the nature of the aneurysm thrombus and the overall anatomy of the aneurysm (Sanchez *et al.*, 1997, Pacanowski *et al.*, 2002b, Vallabhaneni *et al.*, 2003). Device related

factors are also responsible for sac pressurisation and include the porosity of the device, compliance and pulsatility (Faries *et al.*, 1997). When modelling stent-graft drag force it is also extremely important to include the effects of residual sac pressure, presence of stagnant blood and AAA wall characteristics within any calculations (Li and Kleinstreuer, 2006a).

The longitudinal columnar strength of a stent-graft can vary between manufacturers. Many researchers believe that longitudinal columnar support can help opposite proximal migration (Corbett *et al.*, 2010). Additional fixation is provided by the longitudinal stiffness of the stent-graft together with the degree of iliac artery implantation. For a bifurcated or AUI device the importance of these distal seal zones has received relatively little attention in its ability to prevent migration. Heikkinen *et al.*, was first to report on the potential importance of iliac fixation, in their study migration was identified in 10% of patients, all were found to have suboptimal iliac fixation on the post-implantation CT (Heikkinen *et al.*, 2006). In this study, iliac fixation was categorised according to the fixation length which was the distance from the distal iliac limb to the common iliac bifurcation. The study by Heikkinen *et al.*, (2006) failed to take into consideration the CIA diameters, presence of calcification, tortuosity and other potentially influential factors. A more recent publication by Benharash *et al.*, found that suprarenal and infrarenal stent-graft devices may rely heavily on iliac fixation to maintain long-term positional stability (Benharash *et al.*, 2007).

Other individual features of stent-graft configuration may impact on device fixation. Zhou *et al.*, (2007) undertook an *in vitro* comparison of the fixation between a standard stent-graft and one with a single stented fenestration. Zhou and colleagues concluded that the inclusion of a stented fenestration increases the fixation strength ($P<0.001$). With reference to fenestrated stent-grafts Scurr *et al.*, (2008) investigated, using an *in vitro* model,

the ability of different covered and uncovered stents to resist migration of a fenestrated stent-graft (Scurr *et al.*, 2008b). Scurr and colleagues concluded that out of the three stents tested, the Jostent (Abbott Vascular, Abbott Park, IL) provided the greatest resistance to a 50% reduction in cross-sectional area.

3.3 Prevalence of proximal migration in infrarenal stent-grafts

Varying approaches to the detection of migration are likely to explain much of the different reported rates of migration for both thoracic and abdominal stent-grafts. Reports of migration for thoracic stent-grafts vary between 0 to 30% (O'Neill *et al.*, 2006b). Different fixation mechanisms are used for abdominal grafts and this is likely to partly explain the different rates of migration with different devices; however, even with the same infrarenal device there are widely varying reported migration rates: 0 to 21% for the Aneurx graft (Medtronic, Santa Rosa, CA), 2 to 18% for the Talent graft (Medtronic ,Santa Rosa, CA) and 2 to 8% for the Zenith graft (Cook Medical Inc, Bloomington, IN)(Table 3.1).

Migration is typically classified based on pre-established definitions (movement ≥5 mm or ≥ 10 mm). Several reports have sought only to document cases of migration if they result in an associated complication e.g. proximal type 1 endoleak or require reintervention e.g. insertion of a proximal cuff. Such cases of migration are often described as *clinically significant migration* and have been reported as outcomes for some of the major RCTs and stent-graft registries (UK EVAR Trial Participants, 2005, BSET and GLOBALSTAR Collaborators, 2012). In very few instances has the magnitude of stent-graft migration been measured and reported. By way of an example England *et al.*, (2004) reported migration rates for the Talent (Medtronic, Santa Rosa, CA) of mean 4.8 SD 4.2 mm at 2-years. By contrast the early

results from the recent manufacture sponsored ENGAGE registry (Endurant stent-graft, Medtronic, Santa Rosa, CA) indicated that migration was assessed during follow-up but failed to provide a precise definition or any descriptive statistics (Stokmans *et al.*, 2012). This was also similar for the short-term outcome report on the C3 Excluder stent-graft (W.L. Gore & Associates, Flagstaff, AZ)(Smeds *et al.*, 2013). The absence of any device migration was introduced into the discussion section of their report yet there was no indication on the definition used or the assessment method e.g. CTA or radiography.

Table 3.1 Incidence of device migration for conventional (infrarenal) stent-grafts

Device/Study	Author, Year	Year	n	Follow-up, mo	Definition (mm)	Migration (%)
AneuRx	Zarins *et al.*	1999	190	12	ND	6.0
	Cao *et al.*	2002	113	28	≥10	15.0
	Conners *et al.*	2002	49	24	≥5	20.4
	Sternbergh *et al.*	2002	81	26	≥5	8.6
	Tonnessen *et al.*	2008	77	39	≥10	18.2
Talent	Lee *et al.*	2002	40	17	≥10	17.5
	Criado *et al.*	2003	240	13.5	≥5	2.0
	Ouriel *et al.*	2003	39	12	≥10	0.0
	England *et al.*	2004	38	24	≥10	15.8
Zenith	Greenberg *et al.*	2001	301	14	≥5	2.7
	Ouriel *et al.*	2003	144	12	≥10	8.2
	Sternbergh *et al.*	2004	261	12	≥5	2.3
	Tonnessen *et al.*	2005	53	30.8	≥5	7.5
Excluder	Kibbe *et al.*	2003	235	24	ND	1.0
	Ouriel *et al.*	2003	25	12	>10	0.0
EUROSTAR	Mohan *et al.*	2002	2862	1-6 years	>5	3.5

ND-Not defined. n, number of patients.

When considering the haemodynamic forces within the abdominal aorta it is easy to understand why proximal stent-graft migration should be in a caudal direction. There have been a small number of reports suggesting *apparent* cranial migration of the proximal portion of infra-renal stent-grafts (Katzen *et al.*, 2005). The typical scenario is that a completion angiogram is performed demonstrating patent renal arteries. A subsequent investigation reveals renal artery occlusion and, therefore, proximal migration of the stent-graft is assumed. The report from Katzen *et al.* bases this on a catheter angiogram without any CT confirmation. It must be noted that significant renal artery coverage with graft fabric may be present and yet not impair flow immediately after deployment. Unless the image intensifier is aligned optimally with the renal ostia, typically using cranial and oblique angulation, then the operating team may be unaware of this partial renal coverage. When these renal arteries occlude in a delayed manner, as may happen, then it is possible for an erroneous conclusion of proximal stent-graft migration to be made. Unless comparative high quality CT datasets are available at different time points to clearly show movement in relation to aortic reference points, then the inference of cranial stent-graft migration solely based on delayed renal artery thrombosis may be inaccurate.

3.4 Distal iliac limb migration

Changes in the position of the distal iliac limbs can be interpreted as distal iliac limb migration. Distal migration can be calculated in a similar manner to proximal migration using a fixed iliac reference points e.g. hypogastric arteries. Parodi and colleagues initial description of six tubular endografts each had only a single proximal attachment site (Parodi *et al.*, 1991). It was reported that the distal (unattached) end of these tube grafts frequently migrated back into the aneurysm (Thomas and Sanchez, 2009). This is perhaps not surprising

in that blood flow through a curved stent-graft generates traction on both of its ends (Chuter, 2002). Early EVAR aorto-aortic (tube) grafts were particularly prone to distal migration and secondary endoleak. Even some bifurcated stent-grafts have experienced the graft limbs being slowly pulled out of the common iliac arteries (Beebe *et al.*, 2001). As the limbs bent the forces became higher until the limb either thrombosed or popped back into the aneurysm causing an endoleak.

It is clear from the reports both by Beebe *et al.*, (2001) and more recently Tim Chuter, in 2002, that migration of an iliac limb does exist and that there are haemodynamic reasons to explain this. Despite its existence, migration of an iliac limb is scarcely reported within the literature (Alerci *et al.*, 2005, Maleux *et al.*, 2001). This may be due to a lack of association with adverse clinical sequelae. A distal type 1 endoleak is one of the most likely complications from the cranial migration of an iliac limb. However, distal type 1 endoleaks are often thought of as an early complication relating to patient selection or stent-graft deployment issues. These endoleaks are generally treated as part of the primary procedure using either a moulding balloon or extension of the device (Karch *et al.*, 1999). Faries and colleagues reported on their experience of 597 EVAR procedures over a 6-year period (Faries *et al.*, 2003). Distal type 1 endoleaks were reported in 12 (2%) patients, over a series of different time points. All but one of these distal type 1 endoleaks were successfully treated by extension of the iliac limb. Despite the reported incidence, these high-flow type I lesions were not identified as a statistically significant risk factor for rupture in the EUROSTAR registry (Vallabhaneni and Harris, 2001). This may be due to the fact that these endoleaks are easily detected and most commonly managed using an endovascular approach. Confirming the need to treat a distal type 1 endoleak, the EUROSTAR registry did identify

distal type 1 endoleaks as a risk factor for open surgical conversion, risk ratio 2.6 (95% CI 1.3 to 5.3, *P*=0.01) (Vallabhaneni and Harris, 2001). Iliac limb occlusions are also a possible complication from stent-graft migration. Cochennac and colleagues reported on a series of iliac limb occlusions in EVAR patients during a mean 9.5 month follow-up (range, 0 – 71 months). Thirty-three (7.2%) patients experienced an iliac limb occlusion but only one case was attributed to stent-graft migration (Cochennec *et al.*, 2007). Overall there appears to be a relatively low incidence of iliac-related secondary events in patients undergoing EVAR.

There are several factors that are known to influence the stability of the distal attachment sites. Perhaps unsurprisingly, there is some overlap with the risk factors for proximal migration. Stiffness of the stent-graft, curvature of the aorta, the diameter of the CIA, and the length of uncovered CIA have been all been reported as factors (Maleux *et al.*, 1998, Resch *et al.*, 2000, Ebaugh *et al.*, 2002).

3.5 Migration of fenestrated stent-grafts

Fenestrated grafts incorporate the renal and other visceral arteries in the seal zone and therefore caudal migration of the proximal sealing stent could result in catastrophic visceral artery occlusion. The Zenith fenestrated graft (Cook Medical Inc, Bloomington, IN) is based on a composite body design and the fenestrated proximal component is tubular. The distal component incorporates the graft bifurcation where the largest forces act (Howell *et al.*, 2007) and this design is intended to minimise the risk of caudal migration of the proximal component. The bifurcated distal component, subjected to the longitudinal distraction force, may migrate caudally and adequate overlap is needed to allow for this potential distraction. The renal stents contribute to the stability of the proximal component and as previously

stated, experimental data show a significant increase in the pullout force of a fenestrated graft compared to a standard device (Zhou *et al.*, 2007).

Cases of fenestrated stent-graft migration have been identified within the literature (O'Neill *et al.*, 2006a, Ziegler *et al.*, 2007, Scurr *et al.*, 2008a, Verhoeven *et al.*, 2010, Greenberg *et al.*, 2009a, Troisi *et al.*, 2011). In these short and mid-term reports (Table 3.2) device migration was generally poorly defined and rates were based on cases resulting in clinical signs or requiring re-intervention (clinically significant migration). Migration of conventional (infrarenal) stent-grafts is often classified using the SVS/ICVS reporting standards as any movement ≥10 mm or that led to symptoms or required re-intervention (Chaikof *et al.*, 2002a). This definition is likely to be insufficient for fenestrated stent-grafts where smaller movements have been associated with sequelae (Verhoeven *et al.*, 2010).

Table 3.2 Proximal migration rates for currently available fenestrated stent-grafts

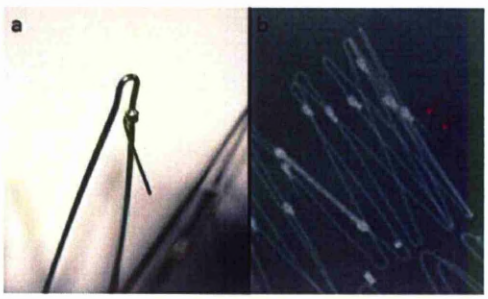
Author(s)	Year	Device	N	Follow-up, months	Migration definition	Migration rate, %
Semmens *et al.*,	2006	Zenith	58	16.8 ± 14.4	CS	3.4
O'Neill *et al.*,	2006	Zenith	119	19 (0-42)	≥ 4mm	0.8
Sun *et al.*,	2006	Zenith	317	17.7 (0-46)	NR	NR
Ziegler *et al.*,	2007	Zenith	63	14 (6-77)	CS	3.2
Scurr *et al.*,	2008	Zenith	45	24 (1-48)	CS	2.2
Kristmundsson *et al.*,	2009	Zenith	54	25 (12-32)	CS	3.7
Greenberg *et al.*,	2009	Zenith	30	24 (1-24)	> 10 mm	3.3
Bicknell *et al.*,	2009	Zenith	29	12 (9-14)	NS	NR
Haulon *et al.*,	2010	Zenith	80	10 (1-38)	NS	NR
Amiot *et al.*,	2010	Zenith	134	15 (2-53)	NS	NR
Verhoeven *et al.*,	2010	Zenith	100	24 (1-87)	CS	1
Triosi *et al.*,	2011	Zenith	96	25 (1-94)	CS	23.5‡
Bungay *et al.*,	2011	Anaconda	4	1 (1-6)	NS	NR
Tambyraja *et al.*,	2011	Zenith	29	17 (8-21)	NS	NR
GLOBALSTAR, BSET	2012	Zenith	318	11 (1-54)	CS	12
Quiñones-Baldrich *et al.*,	2013	Ventana	31	15.6	> 10 mm	3.2
Guo *et al.*,	2013	Zenith	19	6 (1-12)	NS	0.0
Metcalfe *et al.*,	2013	Zenith	42	8 (1-14)	NS	NR

NR – not recorded; NS – not stated; CS – clinically significant. ‡ data contains both branched and fenestrated stent-grafts.

3.6 Prevention and treatment of migration

Manufacturers have been aware of the need to oppose the drag force and a series of stent-graft design features are placed on the stent-graft to help maintain fixation. Such features include friction, barb or hook penetration (Figure 3.14), suprarenal attachment, columnar strength and arterial ingrowth (Li and Kleinstreuer, 2006).

Figure 3.14 Barbs (image a) are incorporated into proximal component of many stent-grafts in order provide additional fixation for the device. Differences between the angle of the barb and the bare suprarenal stent struts, when viewed on abdominal radiography (image b), can provide useful information regarding positional stability. A change in angle could provide an indication of impending migration as shows stress on the fixation system.



Most EVAR preoperative imaging protocols rely on contrast-enhanced CT angiography with three dimensional post-processing for sizing the endograft and planning the procedure. The resulting images are static and may not fully demonstrate the degree of aortic conformational changes during the cardiac cycle. With current high-speed CT scanners the time taken to scan the aneurysm neck is only a fraction of the cardiac cycle and, therefore, the images could be acquired during diastole (minimum diameter) or systole (maximum diameter), or somewhere in between. Following the work by van Herwaarden and colleagues there may be significant changes within the aortic neck during the cardiac cycle

which may lead to improper endograft sizing, with subsequent graft migration, intermittent type 1 endoleaks, and poor patient outcome (van Herwaarden *et al.*, 2006). Herwaarden and colleagues continued to stress the need to consider the role of dynamic imaging tools in the assessment of preoperative aortic morphology and suggested that this could help in the assessment of migration.

Freedom from stent-graft migration will be aided by optimal implantation. Ultimately this depends on the stent-graft delivery system, experience of the operator and real-time image guidance. The attachments sites must be adequately profiled to allow maximum engagement of the endograft. Maximising iliac fixation length has been shown to increase the migration resistance of a stent-graft (Arko *et al.*, 2005) and maximum coverage of the infrarenal aortic neck has been also shown to benefit migration resistance proximally (Cao *et al.*, 2002). The profiling of landing zones for infrarenal stent-grafts typically involves cranial and oblique angulation proximally and caudal and oblique angulation at the iliac landing zones.

The management of migration can be conservative, endovascular or surgical and depends on many factors including the extent of migration, stent-graft device implanted, fitness of the patient and local skills available. Not all migration will produce clinical sequelae or require reintervention. A stent-graft may migrate caudally and then stabilise without falling into the aneurysm sac and subsequently losing its seal. Migration can, however, lead to a seal failure and endoleak and would require secondary intervention. Using data from the EUROSTAR registry Hobo *et al.* (2006) reported that approximately 1.5% of patients will require a secondary procedure as a result of stent-graft migration (Hobo and Buth, 2006).

Data from the more recent UK EVAR trial supports these figures, in this RCT 2.3% of patients required a secondary interventional procedure as a result of migration (Brown *et al.*, 2007).

The endovascular management of proximal migration usually involves the insertion of a proximal cuff extension. If an endograft without barbs has migrated then it is logical to extend proximally with a cuff that has a greater pullout force by incorporating barbs. Proximal extension using a fenestrated cuff may be required if there is an inadequate seal zone in the infrarenal segment. Although fenestrated endografts are now widely used, it must be remembered that working within the confines of a pre-existing stent-graft makes the deployment of a cuff extension difficult. This is largely because of the risk of not having sufficient rotational control of the fenestrated graft which is required to safely position the fenestrations in relation to the target vessels.

A variety of endostaples and endoanchors have been designed to replicate the function of an interrupted aortic suture in maintaining device stability (Deaton, 2012). These devices are still in their infancy and can be deployed during the primary procedure or as a secondary response to treat migration (Perdikides *et al.*, 2012). A more invasive treatment of laparoscopic aortic banding has also been suggested as a treatment for preventing vessel dilatation and stent-graft detachment from the aortic wall (Sonesson *et al.*, 2001). Migration leading to device failure may also be managed with more aggressive open surgical conversion (Brinster *et al.*, 2011). Mortality for open conversion remains high (Kelso *et al.*, 2009) and as a result there are early reports of a less invasive laparoscopic surgical conversion with removal of the original endograft (Lin *et al.*, 2005).

Cranial migration at the iliac attachment sites can be managed by extension with another endovascular graft either to the lower common iliac artery, if there is a suitable landing zone or by graft extension to the external iliac. There have been cases of complex iliac limb migration which required an open conversion (Maleux *et al.*, 2001).

It is not uncommon to see a very small amount of caudal migration of the Zenith graft due to engagement of the downward pointing barbs. The migration distance required for this engagement to occur is typically 3-5mm. The barbs should remain downward pointing after engagement and the fixation force at this point should be much higher. If a graft without barbs migrates then it is possible that the distraction force has exceeded a constant fixation force and the level of concern should be higher in this circumstance. Review of the original infrarenal neck anatomy will sometimes indicate that the stent-graft has settled into a more stable position in a neck that has varying calibre. If there has been minor migration, some clinicians may elect to manage these conservatively. They may opt to increase the frequency of surveillance to 6-monthly review, at this point either the endograft will be shown to have moved into a new stable position or intervention will be mandated because of progressive migration.

3.7 Chapter 3 - summary

Any stent-graft deployed in the aorta faces a constant displacement or drag force (Liffman *et al.*, 2001, Mohan *et al.*, 2002, Morris *et al.*, 2004). Failure of the device to oppose this drag force will result in stent-graft migration (Zhou *et al.*, 2007). For fenestrated stent-grafts migration could result in distortion of the visceral artery stent and consequent loss of vessel patency. This may be in addition to the other serious consequences of migration e.g.

proximal type 1 endoleak or iliac limb occlusion. For a fenestrated stent-graft inclusion of target vessel stents should theoretically reduce the risk of proximal migration (Scurr *et al.*, 2008b, Zhou *et al.*, 2007). Despite this, migration of fenestrated aortic stent-grafts has been reported.

As with any conventional stent-graft, migration of a fenestrated device may be an early or late occurring complication and may or may not necessitate a secondary intervention. There is an absence of data on the incidence, timings and related sequelae for fenestrated stent-graft migration within the literature. Additionally, as with all aortic stent-grafts, migration of fenestrated stent-grafts can occur at both the proximal and distal landing zones and specifically there is an absence of data on the frequency of iliac limb migration. The cause for migration is likely to be multifactorial. Identification of any risk factors is important as this may provide guidance on patient selection, stent-graft configuration and follow-up strategies.

4. A study into the accuracy of CT central luminal line measurements in the quantification of stent-graft migration.

4.1 Introduction

Imaging modality, measurement techniques and the experience of the observer can affect the ability to identify small changes in stent-graft position following implantation. Multi-detector computed tomography, when undertaken to an appropriate protocol, is considered a reasonable method for assessing stent-graft migration (Greenberg *et al.*, 2004b, O'Neill *et al.*, 2006b). There is, however, a wide range (0 to 20%) in the reported incidence of infrarenal stent-graft migration when assessed using CT (England et al., 2004, Cao et al., 2002, Conners et al., 2002, Criado et al., 2003, Sternbergh et al., 2004, Tonnessen et al., 2005). One possible explanation for this variability is the range in the assessment methods used. Historically, migration was assessed using axial CT images mounted on an X-ray viewing box. Improvements in CT and workstation technology subsequently allowed the quantification of stent-graft position using multiplanar reformatted (MPR) images directly displayed on a computer workstation. The assessment of stent-graft migration is difficult using either technique. The main reason for this is the difficulties in performing length measurements along tortuous vessels, which commonly run along the z-axis of the patient (e.g. abdominal aorta and iliac arteries). These limitations are well acknowledged within the literature and are dependent on both the measurement technique and the quality of the CT data (Ota *et al.*, 2005, Rengier *et al.*, 2009).

In the thoracic aorta, outlining the exact position of the stent-graft using a computer generated line drawn through the centre of the aortic lumen (CLL) has been proposed as a

valid method for assessing stent-graft migration (O'Neill *et al.*, 2006b). Around the time of O'Neills report there was a step change in availability of CT technology, MDCT scanners were widely available and examinations commonly consisted of thin-slice CT datasets with excellent contrast enhancement of the arterial tree. From around 2001 onwards it was possible to scan the entire length of aorta, within a single breath hold, and with optimal arterial enhancement whilst maintaining a near isotropic resolution. Using these datasets, techniques had become available which allowed precise measurements along the length of a vessel even in the presence of severe vessel tortuosity or angulation. O'Neill and colleagues (2006) successfully utilised these newer techniques (CLLs) to perform accurate measurements of stent-graft migration in the thoracic aorta. However, no such validation has been made for CLLs used in the abdominal aorta. It should be feasible to monitor changes in abdominal stent-graft position in a similar manner to that reported by O'Neill *et al.*, (2006). If a CLL measurement technique is to be used in the abdominal aorta, then it is essential to generate robust evidence on the accuracy of the technique in quantifying stent-graft migration.

4.1.1 Aims

The purpose of this chapter is to evaluate the accuracy of the CT CLL measurement technique in quantifying stent-graft migration. It is exceptionally difficult to quantify the absolute *in vivo* position of an aortic stent-graft and measure any changes (migration) over time. Direct visual access to the intraluminal aorta is invasive and not practical, for this reason medical imaging examinations have been used as a surrogate for identifying aortic stent-graft position. The true position of a stent-graft cannot be known and only estimated using a clinical test. To address this limitation migration was simulated in a series of aortic phantoms

in order to provide a range of known migrations. Each simulation was subject to a series of CT scans (before and after migration), so that the CLL assessment technique could then be tested using a group of observers. This initial phase of the experiment provided information on both the reliability and reproducibility of the CT CLL measurements. There are obvious differences between CT datasets acquired using aortic phantoms and those from patients. The second phase of this experiment was to evaluate the CT CLL technique using clinical CT scans from patients with aortic stent-grafts implanted. The following aims were met in this chapter:-

Aim 4.1. Quantify the bias (or systematic deviation from the true migration value) for the CT CLL technique when measuring stent-graft migration simulated in phantoms.

Aim 4.2. Report the intra- (within an observer) and inter-observer (between observers) variability for stent-graft migration measurements obtained using a CT CLL technique, from a series of cases of simulated migration using aortic phantoms.

Aim 4.3. Report the intra- (within an observer) and inter-observer (between observers) variability for stent-graft migration measurements obtained using a CT CLL technique using serial CT data, from a series of patients with aortic stent-grafts implanted.

4.2 Materials and Method

4.2.1 Phantom study

A hollow plastic aortic phantom was created from acrylonitrile butadiene styrene using a stereolithography rapid prototyping system. Stereolithography is a system whereby an ultraviolet laser beam is used to selectively polymerise and solidify a photosensitive polymeric plastic liquid. Such a system has been used previously in the creation of aortic phantoms for image analysis (Canstein *et al.*, 2008). The phantom consisted of a hollow aortic neck and two patent side-branches representing the superior mesenteric artery (SMA) and right renal artery (RRA) (Figure 4.1).

Figure 4.1 A 3D computer-aided design (CAD) image of the aortic neck phantom used in the validation of the CT CLL migration measurement technique

A stent-graft either a Zenith (Cook Inc, Bloomington, IN) or a Talent (Medtronic, Santa Rosa, CA) was deployed inside the phantom at a measured distance from each of the

two aortic side-branches. The exact position of the stent-graft was determined by using a small internal ruler (one millimetre major divisions) and by measuring from the apex of one of the wireforms of the bare suprarenal stent relative to the two side-branches. The deployment position was verified once in the anterior, posterior and left and right lateral positions in order to exclude any stent-graft tilt. The phantom was then filled with iodinated contrast medium mixed with gelatine. In order to accurately simulate the density of blood during arterial phase CT angiography, the precise concentration of contrast medium within the gelatine solution was determined. This information had been previously acquired by experimental work (Oshin, 2009). The iodine-gelatine mix contained 2% w/v Visipaque 240mgI/mL (GE Healthcare, Cork, Ireland) and generated a mean aortic enhancement of 280 HU. Aortic enhancement of between 250HU and 320HU has been previously reported within the literature as clinical acceptable for CT angiography examinations (Fischbach et al., 1999). The gelatine was chilled, allowed to set and the phantom was then suspended in a Perspex box containing water. The phantom was then subjected to a MDCT scan which was performed according to a standard clinical EVAR follow-up protocol (Table 4.1). The resultant Digital Imaging and Communications in Medicine (DICOM) imaging data were then sent to a departmental Picture Archiving and Communication System (PACS). Solidified gelatine was then carefully removed from the phantom using warm water and the position of the stent-graft was re-measured and recorded. There were no differences in the pre- and post-gelatine positions of the stent-graft for any of the phantoms. The stent-graft was then displaced downward by traction of the ipsilateral limb with a pair of forceps; the new position was then measured and recorded. The phantom was again filled with the iodine-gelatine mix, subjected to a second CT scan and then the gelatine removed and the stent-

graft position re-verified. This created a single case of simulated stent-graft migration; the procedure was repeated in order to generate a range (n=15) of known but variable stent-graft migrations using a combination of Zenith (n=7) and Talent (n=8) stent-grafts. The Zenith (Cook Medical Inc, Bloomington, IN) and Talent (Medtronic, Santa Rosa, CA) aortic stent-grafts were specifically chosen since at the time of the experiment they were the two most commonly used aortic stent-grafts (Brown *et al.*, 2007). An additional advantage of using the Zenith and Talent devices is that they are different in construction. The Zenith is manufactured from stainless steel and the Talent from a nickel titanium alloy (Nitinol). With differences in construction and materials there are likely to be some differences in the visibility of the devices when using CT.

Table 4.1 CT scan protocol used to generate the phantom CT datasets

Scanner	Siemens Sensation 16
kV	120
Effective mAs	200
Rotation time (sec)	0.5
Detector collimation (mm)	16 x 0.75
Slice thickness (mm)	2.0
Feed/rotation (mm)	24.0
Reconstruction interval (mm)	1.0
Reconstruction Kernel	B30f medium smooth
Field of view (cm)	38.0
Scan direction	Craniocaudal

4.2.2 Clinical study

Following the phantom study a retrospective review of clinical follow-up CT scans was undertaken. A list of patients from a local hospital, who had been treated by EVAR, were made available. Patients were eligible for inclusion if they had a Zenith aortic stent-graft implantation and a baseline (1-month) and a further follow-up CT scan available (≥ 6 months from the implantation procedure). In the event that several follow-up scans were available then the latest CT scan was used (minimum 6 months post-repair). Patients must have been scanned to a standard follow-up protocol (Table 4.2) which was also consistent with the technique described previously in the phantom experiment. For all included studies acquisition followed an intravenous injection of 100 mL ioversol (Optiray 300, Mallinckrodt, Hazelwood, MO) at 5mL/s. Scanning was commenced when the aortic enhancement exceeded 120 HU; this was determined by the in-built bolus tracking function on the CT scanner. Out of the available cohort nine patients were selected at random. Both the number of patients and landing zones assessed were determined by the reading time available for the observers. Each observer was able to commit two half day sessions in order to complete the image analysis. Ethics committee approval was granted (07/Q1502/43) and this allowed the CLL migration measurement technique to be validated using clinical data.

Table 4.2 CT scan protocol used to generate the clinical follow-up CT datasets

Scanner	Siemens Sensation 16
kV	120
Effective mAs	200
Rotation time (sec)	0.5
Detector collimation (mm)	16 x 0.75
Slice thickness (mm)	2.0
Feed/rotation (mm)	24.0
Reconstruction interval (mm)	1.0
Reconstruction Kernel	B30f medium smooth
Field of view (cm)	38.0
Scan direction	Craniocaudal
Patient position	Supine
Oral contrast	No
Intravenous contrast	100 mL Optiray 300

4.2.3 Three-dimensional imaging software

Phantom and clinical CT data were loaded on to a departmental PACS workstation (Kodak Carestream PACS, 10.2, Kodak, Rochester, NY) which had an in-built vessel analysis module. Each individual CT scan was loaded on to the workstation and an observer created a semi-automatic CLL through the aorta. This was done by using the semi-automated centreline algorithms on the workstation. The CLL was then checked by scrolling through the axial, coronal and sagittal reformats to ensure that it travelled through the centre of the arterial

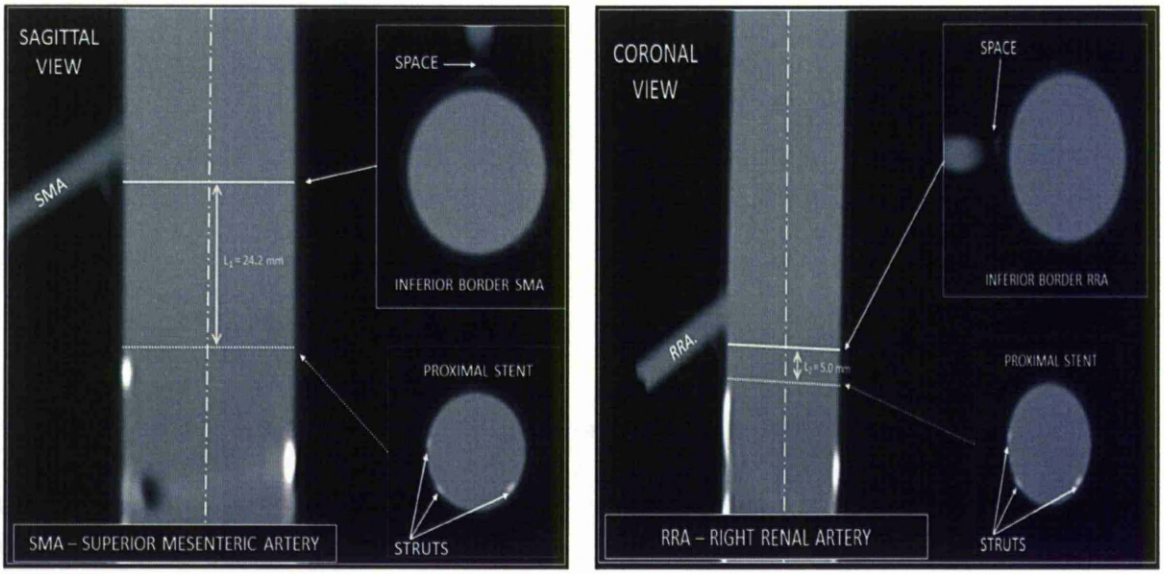
lumen. Oblique axial reconstructions perpendicular to the CLL were displayed in a two dimensional format from which the position of the stent-graft against a reference vessel could be determined.

4.2.4 Measurement protocol

Phantom dataset

A team of three observers independently used CLLs to calculate the stent-graft migration on each of the 15 cases of simulated migration. All observers had previous experience in pre- and post-EVAR CT image post-processing and measurements. Workstation training and clear instructions including measurement definitions and pictorial examples were provided in order to explain the CLL construction process and measurement technique. Using the CT scans obtained using aortic phantoms, the distance between the proximal portion of the stent-graft (first oblique axial CLL reformatted image with two stent struts visible) and the inferior border of each of the reference vessels (L_1 – superior mesenteric artery; L_2 – right renal artery) were recorded using the CLL image (Figure 4.2). The first oblique axial CLL reformat which contained a minimum of two visible stent struts was used to help define the proximal margin of the stent since this helped reduce the risk of selecting calcification over actual stent-graft. The first oblique axial CLL reformat which demonstrated clear separation of the reference vessel (L_1 or L_2) from aortic wall was used to define the inferior border of each reference vessel. Stent-graft migration was then calculated by subtracting the proximal stent-graft to reference vessel position on the 1st CT scan from the same measurement on the 2nd CT scan. All CLL measurements were repeated on two separate occasions by each of the three observers in order to assess intra-observer variability.

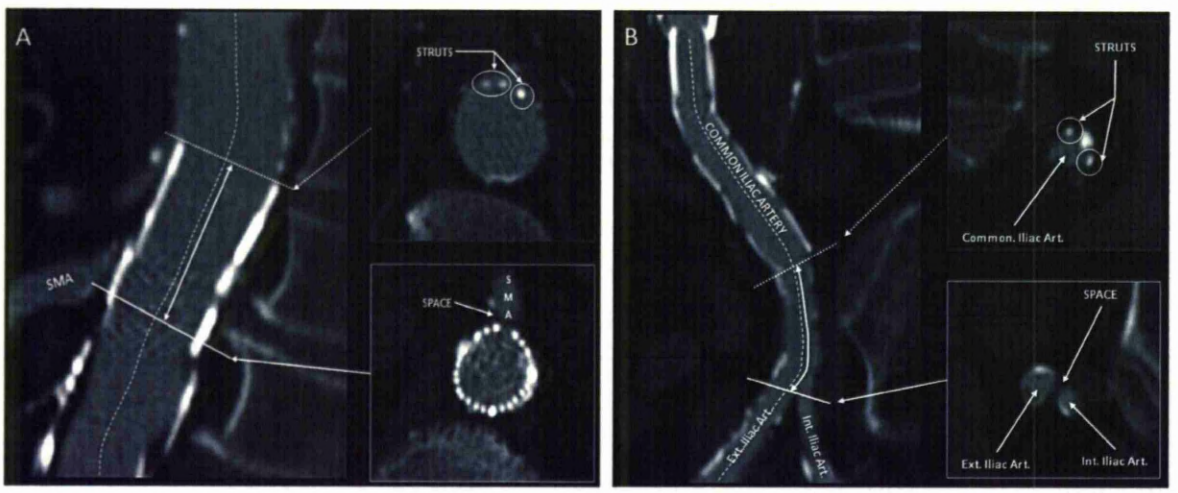
Figure 4.2 CLL images with corresponding oblique axial reformats demonstrating the technique used to record stent-graft position against the superior mesenteric artery (L_1) and right renal artery (L_2). The two lines perpendicular to the CLL correspond to the centre of the reformatted images used to confirm the locations for the two measurement positions



Clinical study

Using the clinical CT scans, evaluation of the proximal and distal landing zones were undertaken in seven and nine patients, respectively. The proximal native vasculature reference point was the superior mesenteric artery (SMA). The distance between the inferior border of the SMA and the first appearance of the stent-graft (two struts) was measured. The inferior border of the SMA was defined as the first oblique axial CLL reformatted image where there is clear separation of the SMA from the aortic wall (Figure 4.3A).

Figure 4.3 A clinical CLL measurement taken at the proximal landing zone of the stent-graft (Image A). The first axial reformatted image, where at least two stents struts were visible (dotted line), was considered indicative of the proximal stent position. The first reformatted slice where there was a clear space between the superior mesenteric artery (SMA) and the aortic wall was considered the inferior border of the reference vessel (solid line). Image B illustrates a clinical CLL measurement taken at the distal landing zone of the stent-graft. The position of the distal stent-graft is recorded relative to the bifurcation of the CIA. The first reformatted slice where there was a clear space between the EIA and the IIA was considered as the iliac bifurcation (solid line). For all CLLs lines drawn perpendicular to the central flow channel demonstrate the projection of each oblique reformat and indicates the central point within each reconstructed slice



The iliac bifurcation was used as the distal reference point for the assessment of iliac limb migration. The iliac bifurcation was defined as the oblique axial CLL reformatted image which first displayed clear separation of the external and internal iliac arteries (Figure 4.3B). Length measurements were obtained using the CLL from the proximal stent-graft to the SMA and from the distal stent-graft to the iliac bifurcation bilaterally using the 1st post-operative CT scan. Each CLL measurement was then compared with the same measurement on the

latest available CT scan. Measurement differences between the two CT scans, for the same anatomical location, would suggest stent-graft migration. All clinical measurements were performed independently by two experienced observers in order to test inter-observer variability. To test intra-observer variability repeat measurements by the same observer were obtained at a different time point (a minimum of one month apart). Any caudal migration of the stent-graft was indicated by a plus sign e.g. +5.1 mm and movement in a cranial direction was indicated using a minus sign e.g. -5.1 mm. Throughout the study CT workstation measurements were recorded using electronic callipers to one tenth of a millimetre.

4.2.5 Statistical analysis

The first aim of this chapter is to assess the accuracy (bias) of the CT CLL technique in quantifying migration (Aim 4.1). For the phantom study, the difference between the CT CLL migration estimate and the actual (true) migration was calculated for each of the simulated migrations. The mean of the differences and the corresponding 95% *limits of agreement* were obtained as described in Bland and Altman (1999).

The following calculations can be applied to both the L_1 and L_2 migration reference vessels. Let us denote d_{a_i} as the true migration and d_i as the CT migration measurement for each phantom simulation i where $i = 1, \ldots . . n$. The mean difference $(\bar{x})$ can then be expressed as:

$$\bar{x} = \frac{\sum_{i=1}^{n} x_i}{n}$$

where

$$x_i = d_i - d_{a_i}$$

and where n is the number of phantom migration simulations ($n = 15$). The standard deviation of the migration difference is calculated using:

$$sd(x) = \sqrt{\frac{\sum_{i=1}^{n}\left((d_i - d_{a_i}) - \bar{x}\right)^2}{n}}$$

Under the assumption that the differences $(d_i - d_{a_i})$ are normally distributed, then it is expected that 95% of the differences would lie within the interval:

$$(\bar{x} - 1.96sd(x),\ \bar{x} + 1.96sd(x)) \qquad (1)$$

whose lower and upper bound are defined as the 95% *limits of agreement.*

Agreement between the CT technique and the actual stent-graft migration can be presented graphically by using the method described by Bland and Altman (1999). For each case of simulated migration the difference between the actual migration d_{a_i} and the CT migration estimate d_i is plotted against the mean of the two values $(d_i - d_{a_i})/2$. This plot is useful in that it shows any extreme or outlying observation; inferences can be made as to whether the differences have a relationship against the mean (i.e. whether the mean difference is greater for large migration distances than smaller).

Furthermore, the precision of the bias estimates can be assessed by calculating the standard errors and confidence intervals. Under the assumption that the data are independent and normally distributed, the variance of $\bar{x}$ can be estimated using $sd(x)/n$, where n is the sample size. The variance of the bias can then be approximated by (see Bland & Altman, 1999):-

$$Var\big((\bar{x}) + 1.96sd(x)\big) = 1.71^2 \frac{sd(x)^2}{n}$$

Therefore, the standard error for $\bar{x} \pm 1.96sd(x)$ is $\frac{1.71sd(x)}{\sqrt{n}} = 1.71SE(\bar{x})$, where $1.71SE(\bar{x})$ is the standard error of the mean difference. In turn, the 95% confidence intervals can be calculated by finding the t distribution with $n = 1$ degrees of freedom. The confidence intervals will therefore, be t standard errors either side of the observer value (See Bland & Altman, 1999).

A similar method was also used to assess variability for intra- and inter-observer measurements for both the aortic phantoms and the clinical CT scans (Aims 4.2 and 4.3). To assess intra-observer variability, Bland and Altman (1999) proposed a similar analysis method to the *limits of agreement* approach. Repeat migration measurements for the same rater, on different occasions, were obtained. For the phantom study one rater (Rater A) undertook CT migration measurements on each of the 15 simulated cases of migration (phantoms) on three separate occasions$\big(d_{1_i}, d_{2_i}, d_{3_i}\big)$. The mean difference for the paired CT migration estimates by the same observer is obtained in the following way:-

As mentioned above, the phantom study involves 3 repeated measurements of each of the 15 simulated cases of migration by each observer. Let us denote d_{1_i} as the CT estimated of migration for measurement set one and d_{2_i} and $d_{3_i}$for measurement sets 2 and 3, respectively, for one observer. Each of the phantom migration simulations is denoted by i where $i = 1, \ldots . . n$. For example, the mean intra-observer difference $(\bar{x})$ for migration based on sets 1 and 2 can then be expressed as:

$$x_i = d_{1_i} - d_{2_i}$$

$$\bar{x} = \frac{\sum_{i=1}^{n} x_i}{n}$$

Where n is the number of phantom migration simulations ($n = 15$). The standard deviation of the difference can then be calculated using:

$$sd(x) = \sqrt{\frac{\sum_{i=1}^{n} \left((d_{1_i} - d_{2_i}) - \bar{x} \right)^2}{n}}$$

Under the assumption that the differences $(d_{1_i} - d_{2_i})$ are normally distributed, then it is expected that 95% of the differences would lie within the interval described by Equation (1). Variability between paired measurements undertaken by the same observer can be presented graphically, using the method described by Bland and Altman (1999). The first paired measurement d_{1_i} and the second d_{2_i} are plotted against the mean of the two values $(d_{1_i} - d_{2_i})/2$. This plot is useful in that it shows any extreme or outlying observation; inferences can be made as to whether the differences have a relationship against the mean (i.e. whether the mean difference is greater for large migration distances than smaller). Confidence intervals for the population mean difference can be described as in Equation (1).

The within-observer standard deviation for CT migration assessments using the phantom data based on the 3 sets of measurements can be estimated from the square root of the residual mean square. In turn this standard deviation can be used to calculate the limits in which we expect the differences by the same rater to lie. Ideally, the differences between two repeat measurements by the same rater are expected to equal zero. The repeatability coefficient (RC) has been defined by the British Standards Institute as the value

below which the difference between paired measurements will lie with a probability of 0.95 (British Standards Institute, 1979). For each rater this can be calculated as follows:-

$$= 1.96 \times \sqrt{\frac{\sum_{i=1}^{15}(d_{2_i} - d_{1_i})^2 + (d_{3_i} - d_{1_i})^2 + (d_{3_i} - d_{2_i})^2}{n-1}}$$

Repeatability coefficients have been calculated for the within-observer variability in both the phantom and clinical element of this chapter. The RC, was further defined by Bland and Altman (1983) and is based on the one-way analysis of variance with the observer as the factor and provides a measure of the precision that represents the value below which the absolute difference between the two repeat measurements by the same observer is expected to lie with a 95% probability after extracting biological variability.

The reproducibility of migration measurements between different raters (inter-observer variability) is also of importance (Aims 4.2 and 4.3). Whilst a repeat measurement by the same rater could show a high repeatability, measurements obtained using direct observations of anatomical landmarks may show variability between raters. For novices this may represent a lack of experience if the measurements were compared to more experienced raters. Such variability differences between raters can be assessed using the *95% limits of agreement* method previously described. For the phantom migration simulations paired observations exist for raters A, B and C. If just the first measurement set for each observer (d) is considered then the mean difference for rater A vs B can be calculated following a similar procedures as described earlier.

Let us denote d_A as the CT assessed migration value for rater A and d_B as the CT migration measurement for rater B, i is each of the phantom migration simulations where $i = 1, \ldots . . n$. The mean difference $(\bar{x})$ can then be expressed as:

$$x_i = d_{A_i} - d_{B_i}$$

$$\bar{x} = \frac{\sum_{i=1}^{n} x_i}{n}$$

Where n is the number of phantom migration simulations $(n = 15)$. The standard deviation of the migration difference between raters A and B is calculated using:

$$sd(x) = \sqrt{\frac{\sum_{i=1}^{n} \left(\left(d_{A_i} - d_{B_i} \right) - \bar{x} \right)^2}{n}}$$

Under the assumption that the differences $(d_A - d_B)$ are normally distributed, then it is expected that 95% of the differences would lie within the interval described by Equation (1).

The agreement between the two raters (A and B) can be presented graphically by using the method described by Bland and Altman (1999). For each case of simulated migration the difference between the CT migration for rate A d_{A_i} and the CT migration estimate for rater B, d_{B_i} is plotted against the mean of the two values $(d_{A_i} - d_{B_i})/2$. This plot is useful in that it shows any extreme or outlying observation; inferences can be made as to whether the differences have a relationship against the mean (i.e. whether the mean difference is greater for large migration distances than smaller). The differences for Rater A vs C can be calculated in a similar manner and also for assessments using the L_2 reference point. Confidence intervals for the population mean difference can be described as in

Equation (1). All analyses described were undertaken using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp, Armonk, NY).

4.3 Results

4.3.1 Migration in aortic phantoms

The mean overall simulated migration was +20.0 (SD, 11.9; range, +2.0 to +39.0) mm (Table 4.3).

Table 4.3 A description of the cases of simulated migration in the aortic phantoms

Simulated Case	Actual Migration, mm (d_a)
1	14
2	35
3	39
4	20
5	2
6	21
7	25
8	6
9	12
10	4
11	15
12	33
13	19
14	37
15	18
Mean	20
SD	11.9
Minimum	2
Maximum	39

For observer A (measurement set 1), the mean difference between the actual (simulated) migrations and the CLL calculated migrations (bias estimate) was +0.4 mm (95% limits of agreement -2.5 mm to +3.3 mm). The estimate of bias was therefore small with a 95%

confidence interval of -0.5 to +1.2 mm. This indicates that the bias of the CLL technique is different from zero although small, and that the range of possibilities is narrow. Similar accuracy was found for observers B and C where the mean difference (together with the 95% *limits of agreement*) were 0.0 mm (-2.8 mm to +2.8 mm) and -0.3 mm (-3.6 mm to +3.0 mm) respectively (Figure 4.4). The confidence interval for the mean difference in these two cases were within the interval (-1.3 mm, +0.8 mm). A full description of the parameters used to report the bias are provided in Table 4.4.

Table 4.4 Bias of the CT CLL migration measurement technique assessed using phantom simulations

		Bias		
		Obs. A	**Obs. B**	**Obs. C**
n		15	15	15
Mean		0.4	0.0	-0.3
Standard deviation		1.5	1.4	1.7
Standard error		0.4	0.4	0.4
Mean, 95% CI	Lower	-0.5	-0.8	-1.3
	Upper	1.2	0.8	0.6
95% LoA	Lower	-2.5	-2.8	-3.6
	Upper	3.3	2.8	3.0
Lower LoA, 95% CI	Lower	-3.3	-3.6	-4.4
	Upper	-1.7	-2.0	-2.7
Upper LoA, 95% CI	Lower	2.4	2.0	2.1
	Upper	4.1	3.6	3.9

LoA, limits of agreement. CI, confidence interval. Obs, observer. All distances are in millimetres. n, number of cases.

The mean paired differences between repeated measurements by the same observer were evaluated on three separate occasions. Mean differences for each of the three observers (measurement set 1 vs set 2) ranged from -0.5 mm to +0.5 mm (95% *limits of agreement* ranged from -2.1 mm to +2.1 mm). Intra-observer variability was highest for observer A (Table 4.7 and Figure 4.5) and the overall repeatability coefficient (RC) for within-

subject paired measurements (all three measurement sets) was +3.2 mm. Inter-observer variability was assessed by calculating the mean paired difference in migration estimates between the two observers (for measurement set 1). The mean paired difference ranged from +0.5 mm to +0.8 mm (95% limits of agreement ranged from -2.4 mm to + 3.3 mm)(Table 4.7 and Figure 4.7).

Based on this data sample, both the accuracy and variability of the CLL migration measurements did not appear to be influenced by the magnitude of migration.

Table 4.5 Intra-observer variability data generated from assessment of the CT phantom data

		Intra-observer variability		
		Obs. A	**Obs. B**	**Obs. C**
n		15	15	15
Mean		-0.5	0.1	0.5
Standard deviation		0.8	0.4	0.8
Standard error		0.2	0.10	0.2
Mean, 95% CI	Lower	-0.9	-0.1	0.1
	Upper	0.0	0.4	1.0
95% LoA	Lower	-2.1	-0.7	-1.0
	Upper	1.2	0.9	2.1
Repeatability coefficient (RC)		3.2	1.1	1.6

LoA, limits of agreement. CI, confidence interval. Obs, observer. All distances are in millimetres. n, number of cases.

Table 4.6 Inter-observer variability data generated from assessment of the CT phantom data

		Inter-observer variability	
		Obs. A vs Obs. B	**Obs. A v Obs. C**
n		15	15
Mean		0.5	0.8
Standard deviation		1.5	1.3
Standard error		0.4	0.3
Mean, 95% CI	Lower	-0.3	0.1
	Upper	1.3	1.5
95% LoA	Lower	-2.4	-1.7
	Upper	3.3	3.3

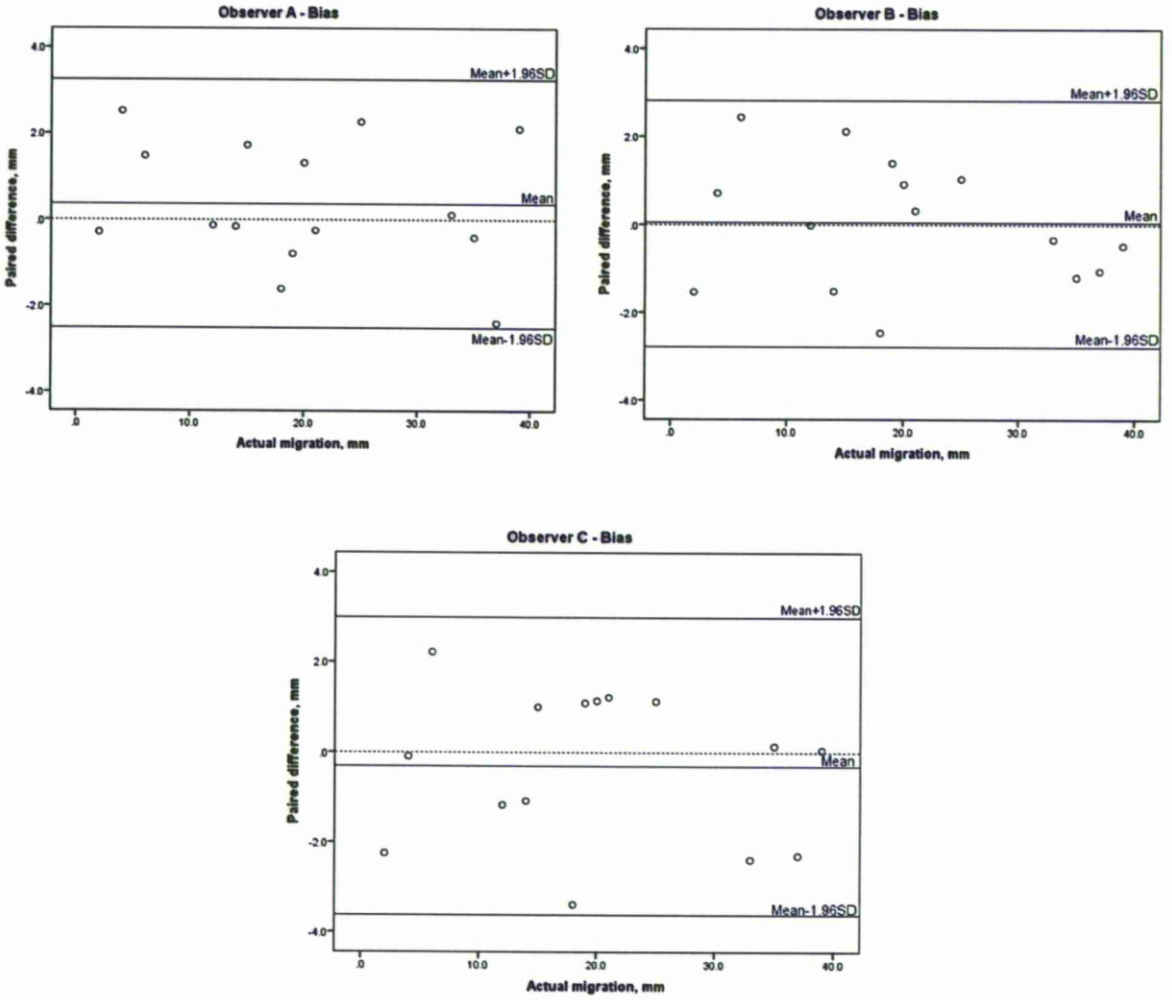
LoA, limits of agreement. CI, confidence interval. Obs, observer. All distances are in millimetres. n, number of cases.

Table 4.7 Intra- and inter-observer variability for the CLL assessment of stent-graft migration (phantom study)

Migration	Intra observer variability			Inter observer variability (Obs. A vs Obs. A)			Inter observer variability (Obs. A vs Obs. C)		
	Lower limit	Mean difference (%)*	Upper limit	Lower limit	Mean difference (%)*	Upper limit	Lower limit	Mean difference (%)*	Upper limit
L_1 : +19.4 [+3.1 to +38.6]	-2.1	-0.3 (-1.5%)	+1.2	-2.9	+0.5 (+2.6%)	+1.5	-1.7	+0.8 (+4.1%)	+3.3
L_2 : +19.6 [+3.4 to +38.7]	-1.5	+0.5 (+2.6%)	+2.4	-1.1	+0.1 (+0.5%)	+1.3	-1.1	-0.4 (-3.1%)	+0.3
Average of (L_1 & L_2) +19.5 [+3.1 to +38.7]	-2.9	-0.2 (+2.6)	+2.5	-1.9	+0.3 (+1.5%)	+2.5	-2.0	+0.2 (+1.0%)	+2.4

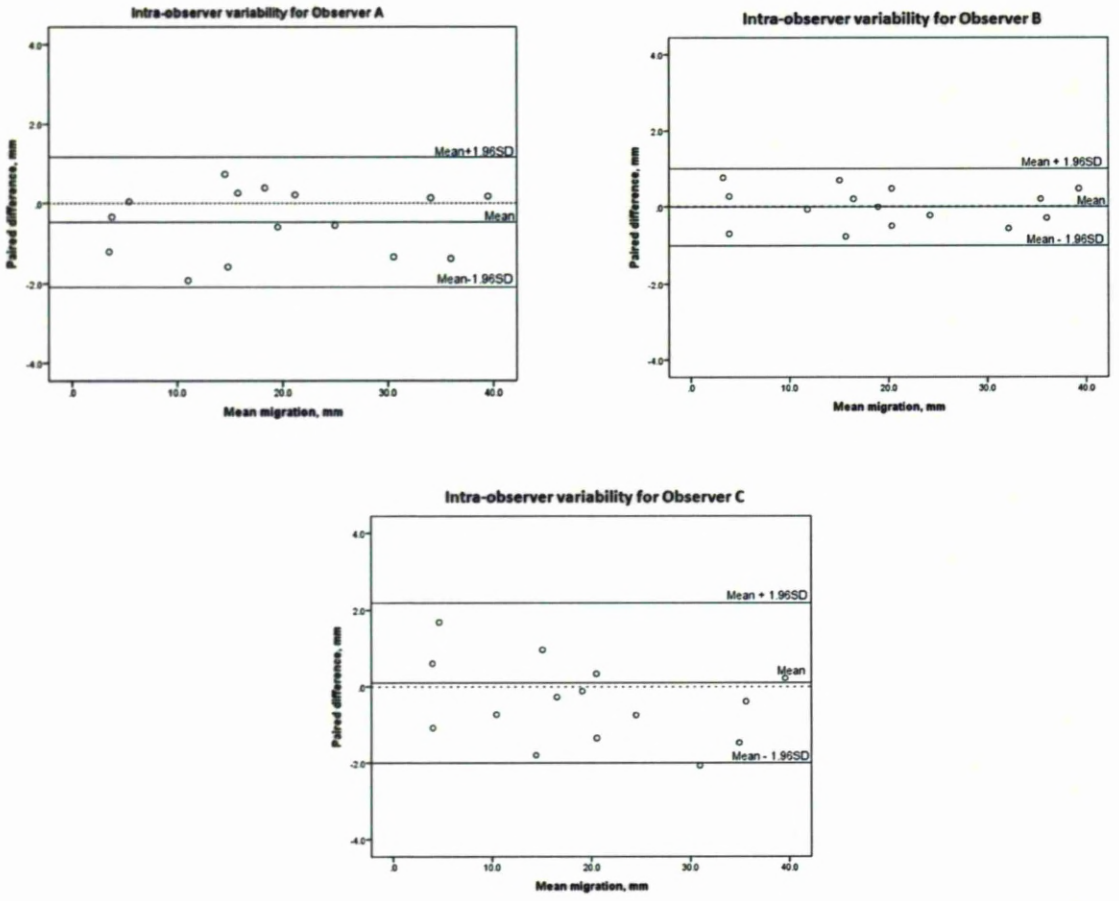
Migration distances are in mm. Variable values refer to the mean value of the 1st measurement of observer A [range]. The upper and lower limits represent the limits of agreement (mean±1.96 standard deviations from the mean difference). *Mean difference expressed as a percentage of the mean value for that variable. Intra-observer variability refers here to the differences between repeat measurements for observer A (measurement set 1 versus 2). Inter-observer variability refers to the differences between the 1st measurements of observer A and observers B/C.

Figure 4.4 Bland Altman plots displaying the bias (Observers A, B & C) for the CLL assessment of stent-graft migration in aortic phantoms



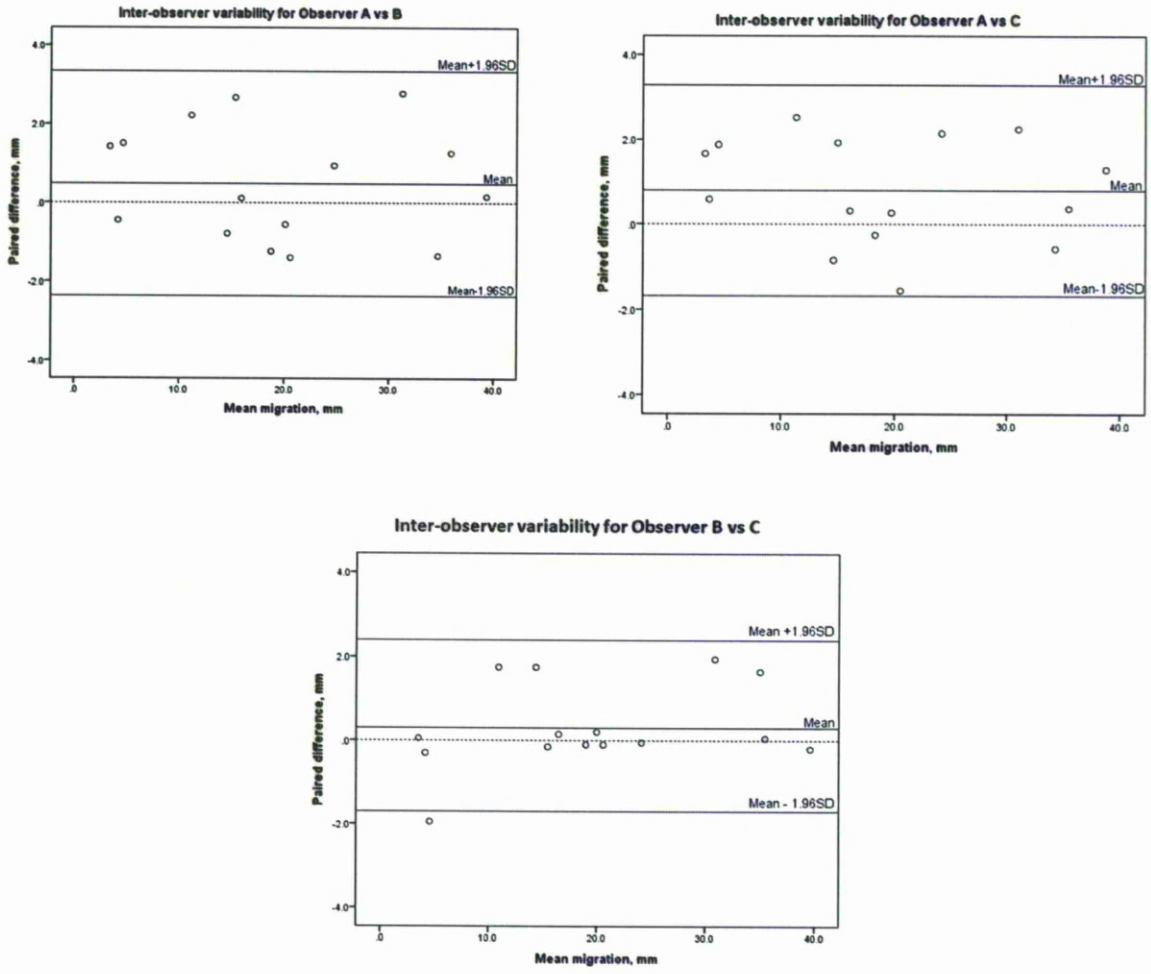
The CLL bias for each observer was determined by calculating the difference between the actual stent-graft migration and the CT determined stent-graft migration using measurement set 1. Limits of agreement (mean±1.96 standard deviations) (outer solid lines).

Figure 4.5 Bland Altman plots displaying the intra-observer variability for the CLL assessment of stent-graft migration in aortic phantoms



Intra-observer variability refers to the differences between repeat measurements of migration by the same observer (Observers A, B & C). The difference between the paired measurements has been plotted against the mean of the paired measurements for each observer (measurement set 1 vs 2). For simplicity, the migration values illustrated are based on average values of L_1 and L_2. Limits of agreement (mean±1.96 standard deviations) (outer solid lines).

Figure 4.6 Bland Altman plots displaying the inter-observer variability for the CLL assessment of stent-graft migration in aortic phantoms



Inter-observer variability refers to the differences in migration measurements between observers. The difference between paired measurements for Observer A and Observer B, Observers A and C and Observers B and C are plotted against the mean of the two measurements rom set 1. For inter-observer variability all calculations were based on measurement set 1 for each observer. For simplicity, the migration values illustrated are based on average values of L_1 and L_2. Limits of agreement (mean±1.96 standard deviations) (outer solid lines).

4.3.2 Clinical stent-graft migration

Clinically, the CLL technique was used to assess changes in stent-graft position in nine patients (median follow-up 37 months, range 24 to 39 months). Migration assessment required the evaluation of 18 follow-up CT scans; this allowed the CLL measurement variability to be assessed in seven proximal and nine distal landing zones. Based on the judgement by observer A (measurement set 1), the mean proximal and distal migration distance in the cohort was + 4.0 (SD, 3.5; range, 0.0 to +11.0) mm and -1.0 mm (SD, 2.4; range, -3.0 mm to +4.0 mm) respectively. When investigating stent-graft migration in patients all (100%) of the paired differences, both between and within observers, were within 4 mm or less of each other. Intra-observer variability was similar to the phantom experiment, mean paired difference between repeat measurements was +0.8 mm (95% limits of agreement -2.1 mm to +3.7 mm) at the proximal margins and -0.3 mm (95% limits of agreement -3.0 mm to +2.5 mm) at the distal margins (Tables 4.8 & 4.10; Figure 4.6). The repeatability coefficient for within-subject measurements was 2.9 mm for proximal measurements and 3.3 mm for distal. Inter-observer variability was again similar with mean paired differences proximally and distally +0.2 (95% limits of agreement -3.4 mm to +3.8 mm) and +0.2 mm (95% limits of agreement -3.7 mm to +4.0 mm) respectively (Tables 4.9 & 4.10; Figure 4.6). With visual inspection of the Bland-Altman plots (Figure 4.6) there was no apparent association between the magnitude of stent-graft migrations and measurement variability.

Table 4.8 Intra-observer variability for the assessment of the clinical stent-graft migration

		Proximal		Distal	
		Obs. A	**Obs. B**	**Obs. A**	**Obs. B**
n		7	7	9	9
Mean		0.8	0.4	-0.3	0.3
Standard deviation		1.5	1.7	1.4	1.7
Standard error		0.6	0.6	0.5	0.6
Mean, 95% CI	Lower	-0.6	-1.2	-1.4	-1.1
	Upper	2.2	1.9	0.9	1.6
95% LoA	Lower	-2.1	-2.9	-3.0	-3.1
	Upper	3.7	3.6	2.5	3.6
Repeatability coefficient (RC)		2.9	3.3	2.8	3.3

LoA, limits of agreement. CI, confidence interval. Obs, observer. All distances are in millimetres. n, number of cases.

Table 4.9 Inter-observer variability for the assessment of clinical stent-graft migration

		Inter-observer variability	
		Proximal	**Distal**
n		7	9
Mean		0.2	0.2
Standard deviation		1.8	2.0
Standard error		0.6	0.7
Mean, 95% CI	Lower	-1.3	-1.4
	Upper	1.7	1.8
95%LoA	Lower	-3.4	-3.7
	Upper	3.8	4.0

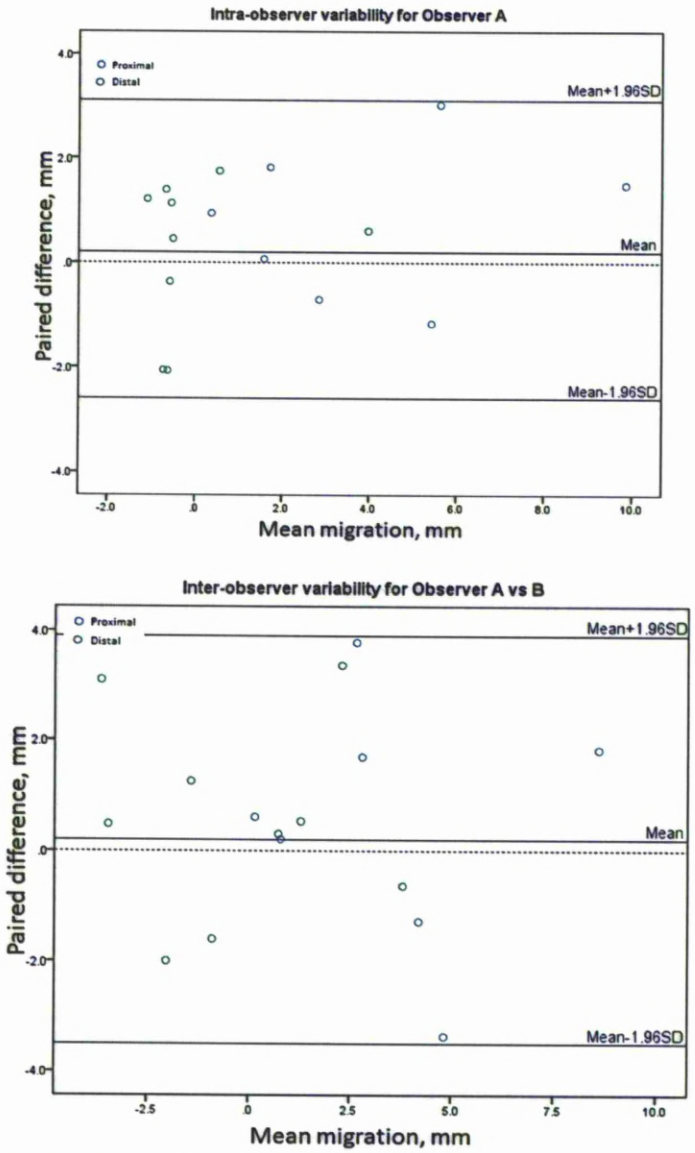
LoA, limits of agreement. CI, confidence interval. All distances are in millimetres. n, number of cases.

Table 4.10 Intra- and inter-observer variability for the clinical CLL assessment of stent-graft migration

Variable	Intra-observer variability			Inter-observer variability (Obs. A vs Obs. B)		
	Lower limit	Mean difference (%)*	Upper limit	Lower limit	Mean difference (%)*	Upper limit
Proximal : +4.0 [-0.1 to +10.6]	-2.1	+0.8 (+20.0%)	+3.7	-3.4	+0.2 (+5.0%)	+3.8
Distal : -0.6 [-4.4 to +4.0]	-3.0	-0.3 (-50.0%)	+2.5	-3.7	+0.2 (-33.3%)	+4.0
Average: +1.4 [-4.4 to +10.6]	-2.6	-0.6 (42.9%)	+3.1	-3.5	+0.2 (+14.3%)	+3.9

Migration distances are in mm. Variable values refer to the mean value of the 1st measurement of observer A [range]. The upper and lower limits represent the limits of agreement (±1.96 standard deviations from the mean difference). *Mean difference expressed as a percentage of the mean value for that variable. Intra observer variability refers to the differences between repeat measurements for observer A. Inter observer variability refers to the differences between the 1st measurements of observer A and observer B.

Figure 4.7 Bland Altman plots displaying the CLL variability, intra-observer (Observer A) and inter-observer (Observer A vs B) for the assessment of stent-graft migration when using clinical CT scans



Intra-observer variability refers to the differences between repeat measurements of stent-graft migration for the same observer (within observer). Inter-observer variability refers to the differences between migration measurements (measurement sets 1) for observer A when compared to observer B (between observers). For both intra- and inter-observer the differences have been plotted against the respective mean of the two comparative measurements. Limits of agreement (mean±1.96 standard deviations) have also been plotted in order to delineated the extremes of any variability (outer solid lines). The migration values illustrated are based on average values of both proximal and distal migrations.

4.4 Discussion

Movement of any aortic stent-graft can have disastrous consequences. Identifying and addressing late device failures before they translate into clinical sequelae may reduce morbidity and mortality. Traditionally, changes in aortic stent-graft position have been assessed by direct review of thick-slice axial CT images. Crude changes in the position of the stent-graft on serial axial CT images were considered indicative of stent-graft migration and may have only been found following during a retrospective review for a related sequela. Improvements in both CT scanner and workstation technology allowed the analysis of stent-graft migration to move forward. Serial MPRs not only allowed the position of the stent-graft to be tracked relative to a fixed landmark but also provided a numerical indication of the magnitude of any displacement. MPRs have led to a more accurate indicator of positional changes but are problematic when attempting to profile tortuous vessels, especially the iliac arteries. Over recent years there was further advancement in imaging technology (O'Neill et al., 2006b, Lumsden et al., 2011, Clough and Taylor, 2013). Modern MDCT now routinely allows for thin-slice (≤2mm) CT acquisitions, achievable within a single breath-hold and with optimum arterial enhancement. Software developments in workstations have provided new opportunities for the three-dimensional analysis of each severe vessel tortuosity. Even with these improvements, there has still been a lack of a validated method for assessing stent-graft migration.

In this chapter a CLL technique was successfully validated under laboratory and clinical conditions for the quantification of abdominal stent-graft migration. The assessment of migration requires the computer-based construction of a CLL together with judgements by the reader on the position of the stent-graft and aortic references points. Using a CLL to

assess stent-graft migration appears to overcome many of the limitations of the traditional assessment techniques (direct axial and MPR review). In validating CLLs, firstly the performance of CLLs was assessed in detecting stent-graft migration in a series of aortic phantoms. The validation experiment established that the bias of the CLL technique is small and insignificant from a practical perspective, with a worst case being over or underestimation of migration by up to 4.0 mm. Observer variability in the phantom experiment was low, limits of agreement are also within 4.0 mm, with all of the within-observer and between-observer paired measurement differences being ≤ 4 mm. On the basis of the phantom experiment, it can be proposed that migration ≥ 4mm, established from CLL calculations is representative of true *in vivo* stent-graft movement and can form the basis for defining stent-graft migration within this thesis. Observer variability for the clinical phase of the study was also low. Limits of agreement for both intra- and inter-observer measurements were within 4 mm, with all of the paired clinical measurement differences ≤ 4 mm.

Within the literature there are limited reports investigating the variability of observer performed CT measurements along the length of a vessel. There are no reports which have sought to quantify the bias and variability of any CT technique assessing stent-graft migration. England et al., (2008) investigated the variability of pre-EVAR CT measurements in 30 patients (England et al., 2008). This study, which involved both radiologists and radiographers, reported an inter-observer mean difference of 6 mm. Measurements of aneurysm morphology were obtained using MPRs and this may offer one explanation for the relative lower levels of agreement when compared to a CLL technique. The authors also noted a lack of standardisation in their measurement definitions which may also explain the

decrease in reproducibility. Oshin et al., (2010) investigated the measurement of target vessel separation prior to fenestrated endovascular aneurysm repair (Oshin et al., 2010). In their study they demonstrated similar mean paired differences but with slightly greater limits of agreement. A major difference in Oshin's study was that they opted to use a CLL technique for some of the vessel length measurements. The conclusion of this study was that the subjective interpretation of anatomical landmarks has a greater role in affecting measurement variability than the choice of measurement technique (MPR or CLL). Ghatwary et al., (2012) more recently reported on the use of the St George's Vascular Institute Protocol for the characterisation of infrarenal abdominal aortic aneurysms (Ghatwary et al., 2012). In their study the measurement of vessel length generated intra- and inter-observer repeatability coefficients of 2.5% to 11%. A CLL technique was used to quantify measurements along the length of a vessel, the authors concluded that the measurement of aortic neck length and CIA length generated the highest repeatability coefficients of all length measurements. This provides further justification for the need to validate a CLL migration measurement technique. Migration measurements typically require a length measurement along the suprarenal aorta and in the common iliac arteries. Based on the report by Ghatwary et al., (2012) these measurements were subject to the greatest variation. The study by Ghatwary et al., (2012) used the CT reconstruction software 3Surgery (3Mensio Medical Imaging B.V., Bilthoven, The Netherlands) which uses a semiautomated CLL construction technique which is similar to that used by the Kodak Carestream system used in this chapter.

When discussing the findings in this chapter both the CT technique and CLL generation process must be considered. In this study CLLs were generated from 2.0 mm

MDCT acquisitions with a soft (B30f) reconstruction kernel. The reconstruction kernel, also referred to as "filter" or "algorithm" within some texts, was described by Yu and Leng as one the most important parameters to affect image quality (Yu and Leng, 2013). Reports have also identified a link with between the reconstruction Kernel and resultant CT measurements (Gierada et al., 2010). This study was limited in that it investigated emphysema measurements on chest CT and not vessel lengths. The size of each voxel will have a role in determining the bias of the technique. Two millimetre CT acquisitions produced a CLL migration assessment bias which was relatively small (all 95% confidence intervals were within (-1.3 mm, +1.2 mm). If the slice thickness had increased to 5.0, 7.5 or 10.0 mm then this may have introduced a more measurable bias. It is also likely that the validation of our CLL technique is dependent on other CT parameters which may also include the reconstruction interval, table pitch and X-ray tube current (signal-to-noise ratio). The actual CLL rendering process could also affect the resultant assessment of migration. Currently, there are a range of techniques for generating CLLs which range from a fully automated technique with no observer input to a manual CLL technique where the user seeds multiple points along the centre of the aorta directly from axial images. The generalisability of the results in this chapter must, therefore, take into account the possibility of differences in CLL generation processes, which may exist between different software packages. All methods of producing CLLs can generate errors, in some instances CLLs may not conform to the central channel of the aorta. For an accurate analysis it is essential that the central path of the CLL is confirmed by visual inspection of MPR images. In this experiment neither the phantom nor clinical CLLs required any manual adjustment. Constructing a CLL reduces some of the human decisions when performing measurements along the lengths of a vessel. Human

input is still required in order to identify the reference points from which to measure the position of a stent-graft; this will be prone to human variance. Defining the start/end of the stent-graft and the reference vessel, although subject to clear definitions is challenging at times, especially in patients with luminal calcification. It is for this reason that observer experience is undoubtedly a contributing factor and training considerations must be factored into any assessment of migration. There are potential differences in the visibility of the proximal and distal margins of different stent-grafts on the oblique axial CT reformatted images. Differences may exist because of variations in the metallic composition of the stent struts or the number of struts at the proximal and distal device margins. CT has an excellent ability in visualising metallic structures; since the assessment of migration requires the identification of identical stent-graft landmarks on serial examinations it is unlikely that the configuration will affect such measurements. Data from the phantom experiment included two devices with differing metallic compositions (stainless steel and nitinol) and a range in the number of proximal (12 vs 5) and distal (7 versus 5) stent struts. This situation allowed the testing of the CLL technique over a wide range of situations.

There are further advantages in the adoption of a CLL technique for assessing stent-graft migration. CLLs are now widely available on both dedicated CT and PACS workstations. With most systems designed around endovascular planning, CLLs displaying the aorta and both iliac arteries can be generated with just a few simple clicks of the mouse. With any post-EVAR surveillance programme efficient image analysis is essential; CLLs can provide a quick and accurate method for assessing stent-graft migration. It must be noted that this did not seek to compare a CLL technique against any of the previously documented CT migration assessment techniques. However, it could be argued strongly that CLLs are a valuable

technique for assessing stent-graft migration and that they are likely to be superior to an assessment based on either acquired axial CT images or multi-planar reformatted images.

The possibility of aortic elongation has been raised briefly within the literature (O'Neill et al., 2006b, Litwinski et al., 2006, Shah et al., 2007) and will be discussed in detail in subsequent chapters of this thesis. It must be considered that it is possible for the SMA to stent-graft distance to increase during follow-up without any changes in the actual position of the fabric markers relative to the renal ostia. Likewise it may be possible for the CIA bifurcation to stent-graft distance to increase without any change in the portion of common iliac artery covered by the limb. If during follow-up there is a change in the CLL distance then a more detailed analysis is warranted. Cross-referencing of the CLL measurements against aortic calcification or non-aortic landmarks should also be considered. With this in mind CLLs can be used as a rapid screening tool for migration with more detailed evaluation in positive or equivocal cases (O'Neill et al., 2006b).

There are limitations when attempting to use static imaging (MDCT) to quantify the position of a stent-graft within a moving (pulsatile) structure. Vos et al.,(Vos et al., 2003) documented up to 1.99 mm of craniocaudal movement of the aneurysmal abdominal aorta when imaged by cine MRI. Whether the stent-graft moves simultaneously within a pulsating aorta is currently unknown. A static stent-graft in a mobile (pulsatile) aorta could lead to pseudomigration, the relationship between the stent-graft and the aortic references vessels could vary during the cardiac cycle and differ between serial CT scans. It is likely that there is some degree of synchronisation in the longitudinal movement of the aorta and endograft. Stent-grafts have various design features which encourage them to remain in a fixed position within the aorta (suprarenal fixation, hooks and barbs, radial and columnar force). A more

detailed understanding of this phenomenon could be obtained by studies involving gated (cine) CT. At the time of this study prospective gated CT had limited availability and the alternative of retrospective gated CT was associated with a high radiation dose (Desjardins and Kazerooni, 2004).

In reporting this experiment, it is accepted that there are other limitations. The use of a plastic aortic phantom may raise questions. This was a simple but morphologically similar replica of the upper abdominal aorta but lacked angulation and tortuosity; many supporters of CLLs describe its benefits when evaluating tortuous vascular systems. Questions may arise regarding the extent of any bias and variability if the aortic phantoms contained some degree of vessel angulation and or tortuosity. The results in this chapter must take into account that the phantom study used stent-grafts deployed in only straight aortic necks. In contrast, the clinical CT scans were selected at random from the available DICOM CT data at a local hospital, this goes some way to validating the CLL technique for all eventualities. In this experiment CLLs were successfully applied to a clinical cohort to assess the proximal and distal landing zones; subsequently there was some variety in the quality of the aortic neck (angulation and calcification) and tortuosity to the iliac arteries. Tilting of the stent-graft may have an impact on the accuracy and variability of CLL migration assessments. In cases with challenging anatomy there is the likelihood of some degree of stent-graft tilt. This experiment did not seek to experimentally evaluate the effect of tilt on the accuracy and variability of CLL measurements and this must be considered when interpreting the data.

Finally, this experiment only sought to evaluate the accuracy of CLLs in quantifying longitudinal stent-graft displacement. With an increase in the number of fenestrated EVAR

procedures performed globally each year a need may arise for a study to evaluate the quantification of aortic stent-graft rotation using radiological imaging.

4.5 Conclusion

In conclusion, the bias from CLL determined stent-graft migration is small and insignificant from a practical point of view. Based on data in this sample there is 95% confidence that the bias is less than 1.3 mm. When using 2.0 mm thick MDCT slices it should be feasible to detect stent-graft positional changes which are ≥ 4 mm. A CLL analysis should not be used in isolation; if migration is suspected then a full and detailed evaluation using all CT imagery must be implemented. Minor measurement variability both between and within observers exists and this should also be factored into any clinical decision making. Within this thesis migration, either proximal or distal (iliac), will now be defined as movement of the stent-graft by ≥ 4 mm.

5. Migration of fenestrated aortic stent-grafts: a single centre experience

5.1 Introduction

Approximately half of all AAA are anatomically unsuitable for standard infrarenal EVAR (Elkouri *et al.*, 2004, Keefer *et al.*, 2010). Complex endovascular techniques, such as fenestrated endovascular repair (FEVAR), have been developed especially for these situations where an inadequate infrarenal aortic neck may preclude the use of standard stent-graft.

Fenestrated stent-grafts are, however, subject to the same haemodynamic forces that have resulted in migration of standard infrarenal EVAR devices (see Chapter 3). Movement at the proximal seal zone of a fenestrated stent-graft could result in loss of alignment between the fenestrations and the target vessel ostia. This may be catastrophic and result in compromise of blood flow to the target vessels and or loss of an aortic seal.

Early identification of any migration is critical, recognition can alert the clinician to the presence of device instability and may allow early reintervention, which may avert serious clinical sequelae (Greenberg *et al.*, 2004b). Migration of a fenestrated stent-graft has been previously reported (O'Neill *et al.*, 2006a, Ziegler *et al.*, 2007, Scurr *et al.*, 2008a, Verhoeven *et al.*, 2010, Troisi *et al.*, 2011). In these short and mid-term efficacy studies, device migration was generally poorly defined and rates were based on cases resulting in clinical signs or requiring reintervention.

For standard infrarenal stent-grafts migration is often classified using the SVS/ICVS reporting standards as any movement ≥1.0 cm or that caused symptoms or required

reintervention (Chaikof *et al.*, 2002b). Even back in 2004, Greenberg and colleagues, argued that such a wide definition was insufficient and that adopting a smaller criterion would lead to improvements in patient selection and device modifications by the manufacturer. Such improvements would then hopefully help drive down the incidence of fixation failure. For fenestrated stent-grafts, a smaller definition is even more of a necessity since, smaller graft movements (e.g. 3 mm) have already been associated with adverse clinical sequelae (Verhoeven *et al.*, 2010). It is now possible to revise the SVS/ICVS reporting standards and adopt a shorter definition of migration. Data from the previous chapter and its resultant publication (England *et al.*, 2012) confirmed that MDCT, when combined with a validated measurement technique, can facilitate the more subtle quantification of device migration.

The concept of distal iliac limb migration has almost escaped the attention of many researchers. Cephalad forces act on the distal iliac limbs (Melas *et al.*, 2010) and can induce migration at the distal landing zones. In addition, Alerci *et al.*, (2005) reported that distal iliac limb migration, although infrequent, can occur at any point during follow-up. Together with proximal fenestrated stent-graft migration the incidence and consequences of iliac limb migration are not well understood.

5.1.1 Aims

Based on FEVAR experience from a single institution (Hospital A) this chapter quantified the extent of migration of fenestrated aortic stent-grafts. This data collection and analysis also served as a pilot in order to inform and justify the design of the larger multicentre investigation presented in the next chapter. The aims of this chapter are to:-

Aim 5.1. Quantify the incidence of migration of the Zenith fenestrated aortic stent-graft.

Aim 5.2. Report the timings for proximal and distal (iliac) limb migration.

Aim 5.3. Investigate and report the associated (related) clinical effects of both proximal and distal stent-graft migration in patients treated with a Zenith fenestrated stent-graft.

5.2 Materials and methods

5.2.1 Study design and patient sample

This was a retrospective review of prospectively collected data for all patients treated for short necked and juxtarenal AAAs using a custom-designed fenestrated device based on the Zenith system (Cook Inc, Bloomington, Ind) in a single institution. Research ethics approval was obtained (07/Q1502/43) and patients were considered for inclusion, if they had a fenestrated device implanted between the start of the fenestrated programme in 2003 and 2010. Patients were required to have had a baseline post-operative CT scan (1^{st}) and, at least, one additional follow-up CT scan (minimum of 5 months from the baseline) available in Digital Imaging and Communications in Medicine (DICOM, National Electrical Manufacturers Association, Rosslyn, VA) imaging format.

5.2.2 Image acquisition and reconstruction

Follow-up imaging studies were typically undertaken within 1 month, then at 6 and 12 months, and then annually thereafter. MDCT studies of the abdomen and pelvis were acquired using a Siemens Somatom Sensation 16 (Siemens, Erlangen, Germany). Collimation was set to 2.0 mm with a 1.0 mm reconstruction interval. All acquisitions followed an

intravenous injection of 100mL ioversol (Optiray 300, Mallinckrodt, Hazelwood, MO) at 5mL/s and were initiated using bolus tracking software. Aortic enhancement at the level of the 12th thoracic vertebra must have exceeded 120HU. Data were reconstructed using a B20f kernel and transferred to a CT workstation (Kodak Carestream PACS, 10.2, Kodak, Rochester, NY) for analysis. In essence, this protocol mirrored the clinical CT protocol used in the validation experiment (Chapter 4, Table 4.2).

5.2.3 Migration definition

The definition of stent-graft migration was derived from experimental work (Chapter 4) using a combination of aortic phantoms and clinical CT data. The experiments in the previous chapter included an assessment of bias and intra- and inter-observer variability. In summary, migration was defined as cranial or caudal movement of the device, relative to a vascular landmark of ≥ 4 mm. Migration assessments included an evaluation of both the proximal and both distal (iliac) landing zones. Component separation was not considered as migration but was defined as any movement between the proximal (fenestrated) tubular component and the distal bifurcated part.

5.2.4 Migration analysis

A central luminal line (CLL) was created using the semi-automated CLL algorithm on the workstation. The location of the CLL within the central channel of the vessel lumen was confirmed by scrolling through multi-planar reformatted images. Reconstructions perpendicular to the CLL were also evaluated in order to confirm exact locations when undertaking measurements from the CLL images (Figure 5.1). The proximal native vascular reference point was the superior mesenteric artery (SMA). The distance between the inferior

border of the SMA and the first appearance of the stent-graft (two struts) was measured. The inferior border of the SMA was defined as the first oblique axial CLL reformatted image where there was clear separation of the SMA from the aortic wall (Figure 5.1A). The iliac bifurcation was used as the distal reference point and was defined as the first oblique axial CLL reformatted image, where there was clear separation of the internal and external iliac arteries (Figure 5.1B). Length measurements were obtained, using the CLL to measure from the proximal stent-graft to the SMA, and from the distal extremes of the stent-graft to the iliac bifurcation (bilaterally) using the 1st post-operative CT scan (baseline). Each CLL measurement was then compared with the same measurement on all available subsequent CT scans. Measurement differences between the baseline and subsequent CT scans, for the same anatomical location, would suggest device migration. Caudal migration of the stent-graft was indicated by a plus sign (e.g. +4.1 mm) and movement in a cranial direction was indicated using a minus sign (e.g. -6.4 mm). CT workstation measurements were recorded using electronic calipers to 1/10 of a millimetre.

Using the CLL data, any patient meeting our definition of device migration was subjected to further scrutiny. This included visual analysis of the reconstructed aortic segment from which specific landmarks were identified within the aortic wall (e.g. calcification). These images, in addition to the CLL data, were assessed by two observers in order to confirm whether the device had migrated with respect to its initial implanted position. Examples of images used in the further scrutiny of cases of quantifiable migration are illustrated in Figure 5.2 and Figure 5.3.

Figure 5.1 An illustration showing the measurement of proximal and distal stent-graft migration. For proximal migration (Image A) the first oblique axial reformatted image, where at least two stents struts were visible (circles), was considered indicative of the proximal stent position. The first reformatted slice where there was a clear space between the superior mesenteric artery (SMA) and the aortic wall was considered the inferior border of the reference vessel (arrow). Distally (Image B), the position of the distal stent graft is recorded relative to the bifurcation of the common iliac artery. The first oblique axial reformatted image where at least two iliac stents struts were visible was considered indicative of the distal stent position (circles). The first reformatted slice where there was a clear space between the external iliac artery and the internal iliac artery was considered the level of the iliac bifurcation (arrow). For both landing zones the distances between the two reference points were measured (d_b) and compared between serial CT scans

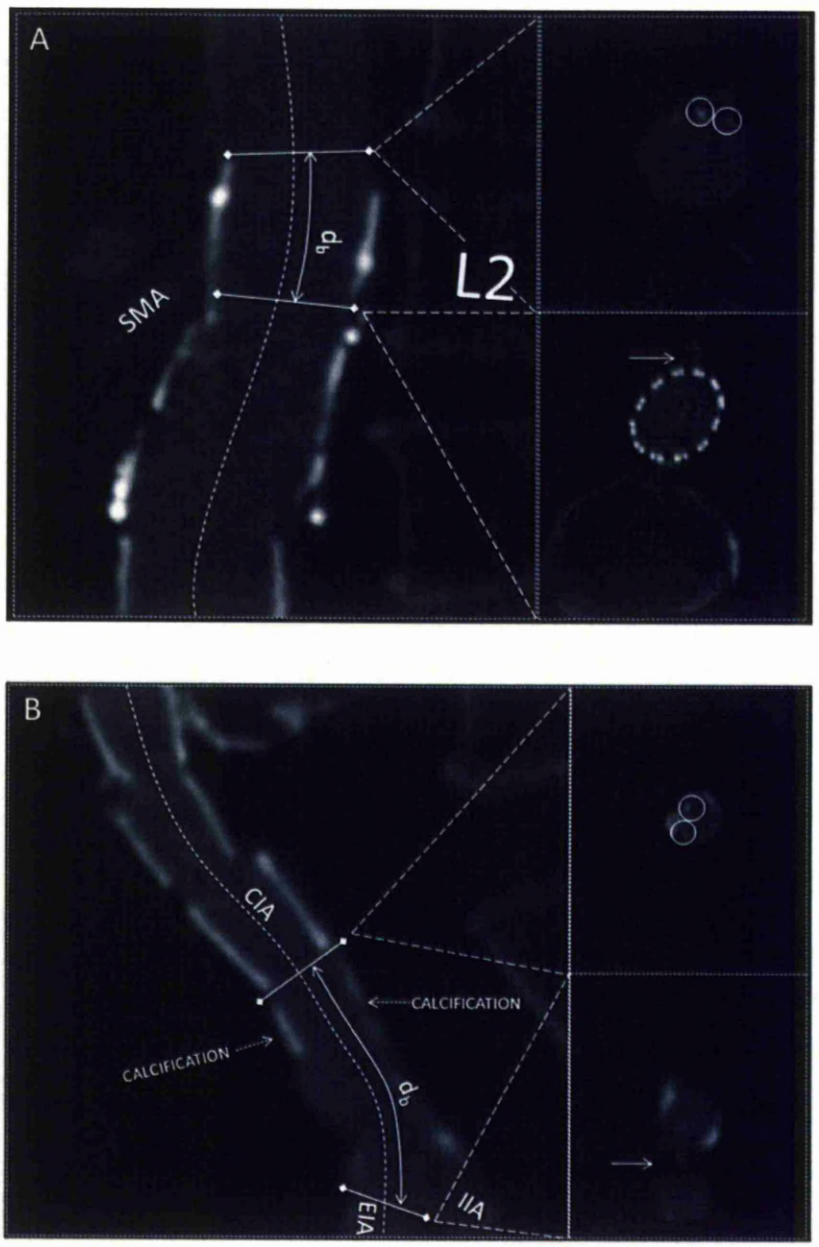


Figure 5.2 CLL image from the 2004 1st post-operative follow-up CT scan (a), the proximal portion of the fenestrated stent-graft was 24.5 mm above the inferior border of the SMA. On the 2004 3D volume rendered (VR) image (b) the top of the bare stent struts were in line with the origin of the coeliac axis (arrow). By 2011 the stent-graft had moved caudally 8.0 mm, the proximal margins of the device are now resting 16.5 mm above the inferior border of the SMA (c). On the 2011 3D VR image (d) there is clear evidence of caudal migration with an absence of stent graft covering the infracoeliac aorta (arrow)

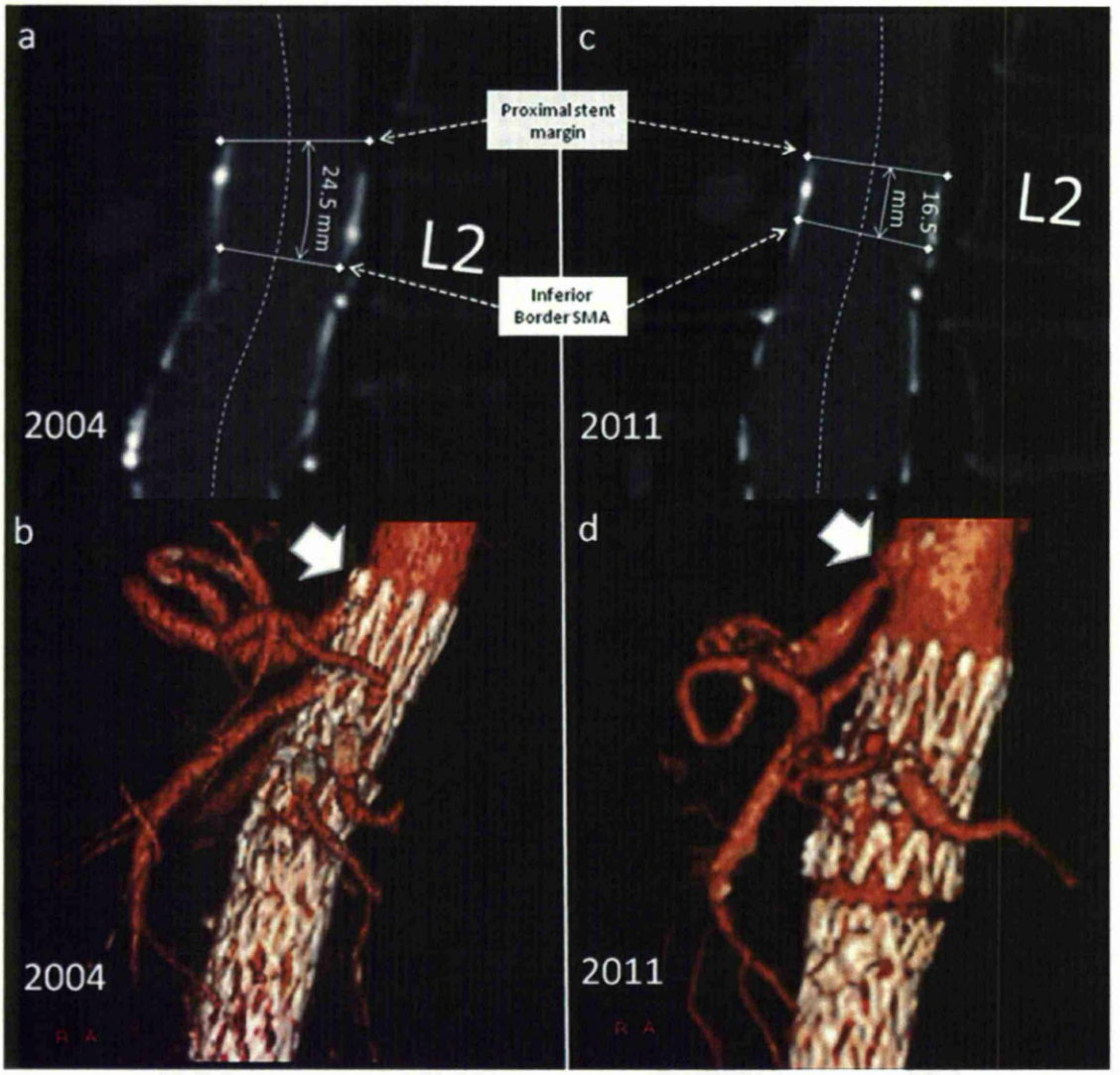
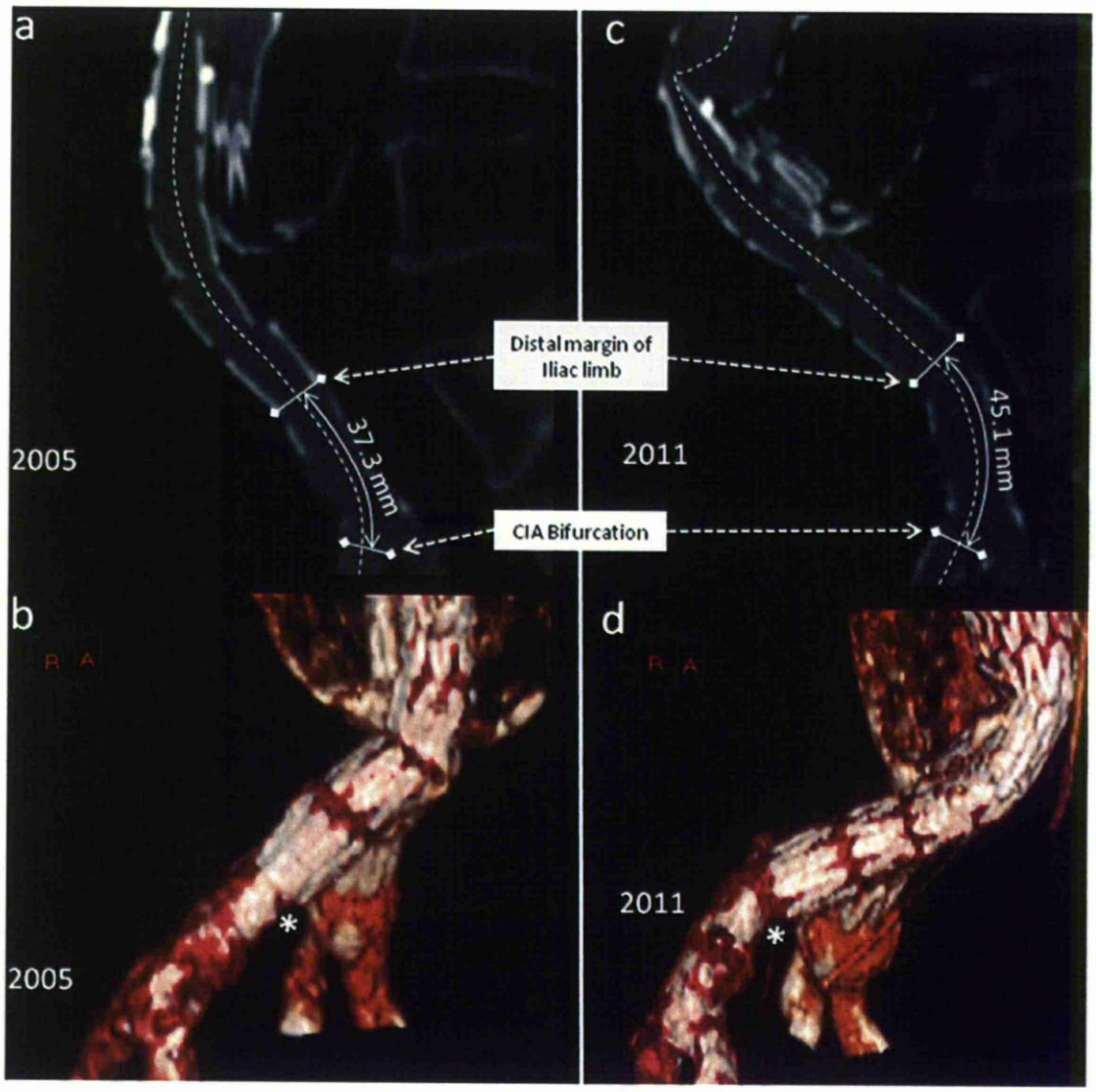


Figure 5.3 CLL (a) and 3D VR images (b) from the 2005 1st post-operative follow-up CT scan, the distal portion of the left iliac limb was sitting 37.3 mm above the bifurcation of the right common iliac artery. By 2011 the limb had moved cranially 7.8 mm, the distal margins of the device are now resting 45.1 mm above the common iliac artery bifurcation (c). On the VR images (d) cranial movement of the device between the two time points can clearly be seen in relation to vascular calcification (*)



5.2.5 Statistical analysis

Initial statistical analyses were undertaken using SPSS for Windows Version 21.0 (IBM Corp, Armonk, NY). More detailed survival analyses were conducted using the statistical programming language R 2.2.1 (R Development Core Team, 2005), which included the use of the Survival (Therneau, 2013) package. In order to satisfy Aims 5.1, 5.2 and 5.3, descriptive statistics were first used to report proximal and distal migration data. A normality test based on the Shapiro-Wilk approach (Shapiro and Wilk, 1965) was carried out, if the corresponding P value was greater or equal to 0.05 (i.e. the null hypothesis that the data followed a normal distribution is not rejected at the 5% significance level), then the mean and standard deviation were reported as summary measurements. If the Shapiro-Wilk normality test produced a P-value <0.05, then these data were considered to be not normally distributed and median values together with the corresponding inter-quartile ranges (IQR) were reported. When describing the magnitude of migration (distance), descriptive statistics were generated only for those patients who met the migration definition (≥ 4 mm). Frequencies and their relevant percentages were also reported for migration (Aim 5.1) based on the validated definition (≥ 4 mm) at both the proximal and distal landing zones. The incidence of stent-graft migration (proximal and distal) was also reported by reflecting the overall sum of follow-up data. The frequency of a disease or event (complication) is often, from an epidemiological perspective, reported in person-years (Wood *et al.*, 1997).

For categorical variables statistical significance was calculated using the Chi-square test (which may include the linear-by-linear association test) or the Fisher's exact test. The linear-by-linear association Chi-square (or the Mantel-Haenszel test for linear association) test is an ordinal measure of significance, which is preferred when testing the significance of

linear relationship between ordinal variables (Agresti, 1996). The *t* test was used to assess statistical significance in continuous variables that were approximately normally distributed. For those variables that were not normally distributed, the Mann-Whitney U test was used, P values <0.05 were considered statistical significant.

Kaplan-Meier methods with and without interval censoring were used to construct survival curves for proximal, distal (iliac) and any device migration (Aims 5.2). In standard time-to-event or survival analysis, individuals are followed over time for the occurrence of a specific event (e.g. death). If the event is observed then the event is recorded as the time the event occurred, *T*, and the censoring indicator δ would take the value 1. If by the end of the period of study the event has not been observed, the observation would statistically be considered to be right-censored. The value of *T* would be set to the last observation time and δ would take the value 0. When the event is directly observed or is right-censored then there are numerous parametric, semi-parametric and non-parametric methods for estimating survival curves and for both hypothesis testing and the modelling the effects of covariates (Lindsey and Ryan, 1998). For stent-graft migration the precise time of the event is often unknown. Migration is generally asymptomatic and will occur within an interval of time between two serial CT scans. As an example, migration may not be appear on the 1st post-operative CT scan but could be present by the next (6-month) CT scan. In this case, *T* will fall within the time interval between 1st post-operative and the 6-month CT scan. Events which occur between two time points are known as interval-censored data (Lindsey and Ryan, 1998). Commonly available statistical packages e.g. SPSS cannot accommodate these kinds of data. One option is to assume that the event occurred at the beginning, midpoint or at the end of an interval and then apply standard methods for

analysing time-to-event data (Lindsey and Ryan, 1998). Such techniques can, however, lead to bias and potentially misleading results (Rucker and Messerer, 1988, Odell *et al.*, 1992, Dorey *et al.*, 1993). Estimations of survival can be calculated, whilst taking into account the uncertainty in the precise time of the event, using non-parametric maximum likelihood estimations (Finkelstein, 1986, Goetghebeur and Ryan, 2000). To facilitate the latter approach, survival data were computed with the statistical programming language R. For the data presented within this chapter, estimations of migration free survival were generated using the following event time definitions: beginning of the interval, midpoint of the interval, end of the interval and also using an interval censored approach. Survival differences between individual iliac limbs (ipsi- and contralateral) were displayed using Kaplan-Meier curves. Differences between the limb types were assessed by visual inspection of the curves.

The effect of stent-graft migration on the incidence of complications and secondary interventional procedures were also investigated (Aim 5.3). Complications are often referred to as the Achilles' heel of EVAR and can arise for a variety of reasons, including stent-graft migration (Pacanowski *et al.*, 2002a, Tang and Boyle, 2011). The site of migration either proximal or distal (iliac) can influence the type of complication. All images included in the analysis were reviewed for the presence of complications and there are well-recognised reporting standards available for documenting these (Chaikof *et al.*, 2002a, Boyle *et al.*, 2011). Local endovascular databases were also reviewed in order to further establish the presence or absence of any complications. Using the previous review of the literature (Chapters 2 and 3), it has been identified that migration-related complications may lead to ischaemia (regional e.g. renal), aneurysm reperfusion or structural integrity issues e.g. component fracture. It is also important to evaluate follow-up imaging and patient records

for any potentially new complications. A full list of the complications assessed within this thesis is described in Table 5.1, this list will also be relevant to the multicentre data presented in the next chapter. Although not identified within the tables or explicitly defined endpoints the incidence of post-treatment aneurysm rupture and any aneurysm-related mortality were investigated and reported within this thesis.

Table 5.1 Complications assessed within this thesis

Proximal		
Aneurysm reperfusion	***Ischaemic***	***Structural***
Endoleak 1-Proximal	TV compromise	Component fracture
Endoleak III	Limb thrombosis	Kinking
Distal (iliac)		
Endoleak 1-Distal	Iliac limb occlusion	Component fracture
		Kinking

TV, target vessel. Further details on the exact definition of endoleaks can be obtained from (White *et al.*, 1998, White et al., 1997, Ziegler *et al.*, 2007)

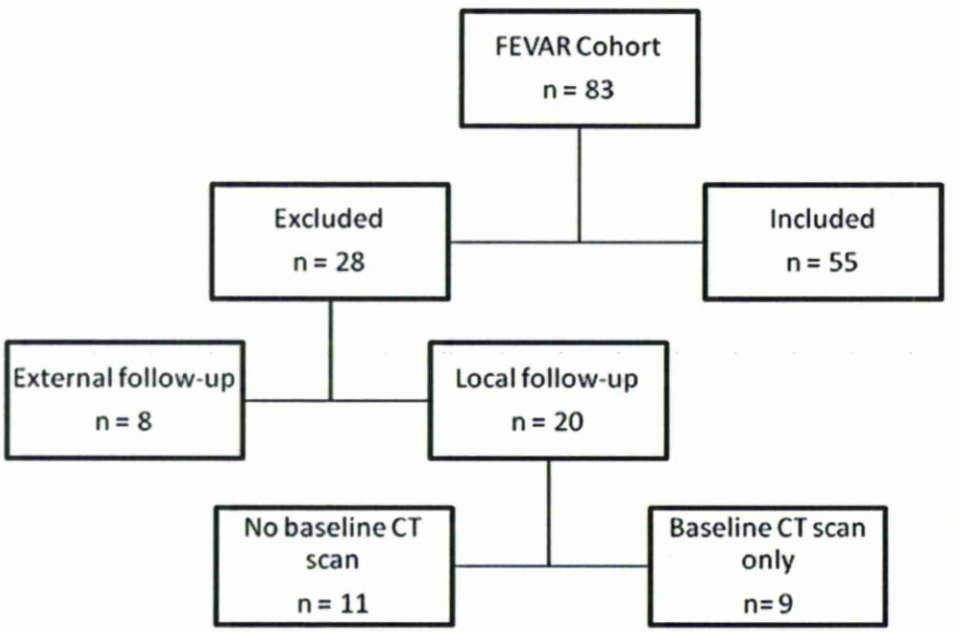
Many complications of FEVAR related complications can be managed conservatively, often by the use of surveillance imaging. For some patients, surgery or an endovascular procedure will be required in order to maintain long-term procedural success and prevent aneurysm rupture. Hospital records were also reviewed in order to identify any migration-related reinterventions within the sample. Typical reinterventional procedures have been described by Triosi and colleagues, which may include open surgical conversion, implantation

of an additional stent/stent-graft, use of a suturing or stapling device or surgical by-pass (Troisi *et al.*, 2011). These methods for identifying and reporting of reinterventions are also relevant for the multicentre data presented in the subsequent chapter.

5.3 Results

A total of 83 patients with juxtarenal AAA were treated at Hospital A with a fenestrated stent-graft. Eight patients were followed up in other hospitals and have, therefore, been excluded from the analysis. Other losses are summarised in Figure 5.4. Overall, there were a total of 55 patients included in this analysis, 49 (89%) men and 6 (11%) women with a mean age of 74 SD 7 years. Preoperative co-morbidity and risk factors for both the included and excluded patients are listed in Table 5.2. Eighteen (33%) patients died during follow-up, review of local vascular databases and hospital computer records indicated that none were considered to be aneurysm-related.

Figure 5.4 Study inclusions and losses



Median maximal AAA diameter was 65 (IQR, 59 to 73) mm. The total number of fenestrations was 162, including 104 renal artery fenestrations, 47 SMA fenestrations and 11 coeliac artery fenestrations (Table 5.3). The most common combination included two small fenestrations for the renal arteries and a scallop for the SMA.

Table 5.2 Study group demographics and risk factors

Patient characteristics		*Inclusions* (n = 55)	*Exclusions* (n = 28)	*P* Value
Mean age (years)		74 SD 7	71 SD 8	0.14
Hypertension		30 (55%)	14 (50%)	0.44
Diabetes		5 (9%)	4 (14%)	0.36
Coronary artery disease*		32 (58%)	15 (54%)	0.43
Cerebrovascular disease†		8 (15%)	6 (21%)	0.31
Renal insufficiency§		8 (15%)	4 (14%)	0.63
ASA Grade$^{\Omega}$	II	14 (25%)	8 (29%)	0.96 [0.79]
	III	39 (71%)	19 (68%)	
	IV	2 (4%)	1 (4%)	
AAA diameter (mm)		65 IQR 59 to 73	63 IQR 58 to 73	0.65

*Previous myocardial infarction, angina or ECG evidence of ischaemia. †Previous stroke or transient ischaemic attack. §Pre-operative serum creatinine > 150 μmol/L. IQR, inter-quartile range. $^{\Omega}$ P values reported were the Chi-square test [Mantel-Haenszel test for linear association]. SD, standard deviation. IQR, inter-quartile range.

Table 5.3 Configuration of scallops and fenestrations used within the study group

	Un-stented		*Stented*	
	Scallop	*Fenestration*	*Scallop*	*Fenestration*
CA	11			
SMA	33	1		13
Renal	3		4	97

CA, coeliac axis; SMA, superior mesenteric artery.

Proximal migration

Of 55 patients with a median follow-up of 24 months (IQR, 13 to 49; range, 5 to 97 months), 10 (18%) showed CT evidence of proximal migration (≥ 4 mm). Of the patients which met the definition of migration, the mean migration was +5.5 (SD 1.4, range +4.0 to +8.1) mm. All proximal migrations were caudally directed. Those cases of proximal migration that met the thesis definition, are presented in a histogram (Figure 5.5). Timings of proximal migration (based on the 1st CT diagnosis of migration) have also been plotted (Figure 5.6). Based on a follow-up of 130.2 person-years, there was a proximal migration rate of 1 migration per 12.5 person-years of follow-up. Kaplan-Meier survival analysis, using interval censoring, estimated that the probabilities of being free from proximal migration at 12 and 36 months, were 91% (95% CI 83% to 100%) and 78% (95% CI 66% to 93%) respectively. For proximal migration, comparison of Kaplan-Meier survival curves using alternative event time definitions are summarised in Table 5.4 and illustrated in Figure 5.7.

Figure 5.5 Frequencies of proximal stent graft migration

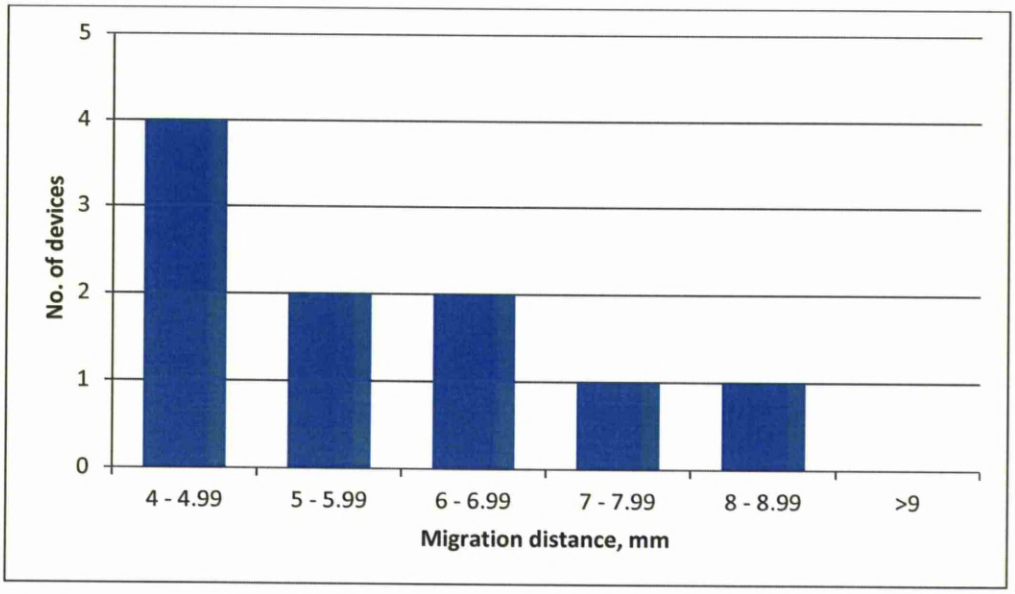


Figure 5.6 Time to 1st CT diagnosis of proximal migration

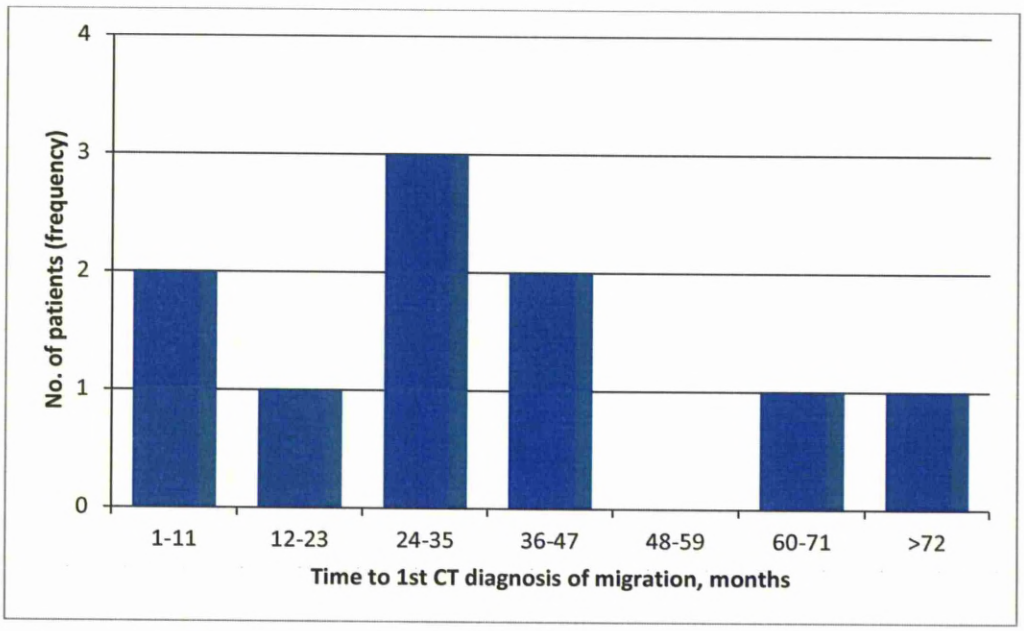


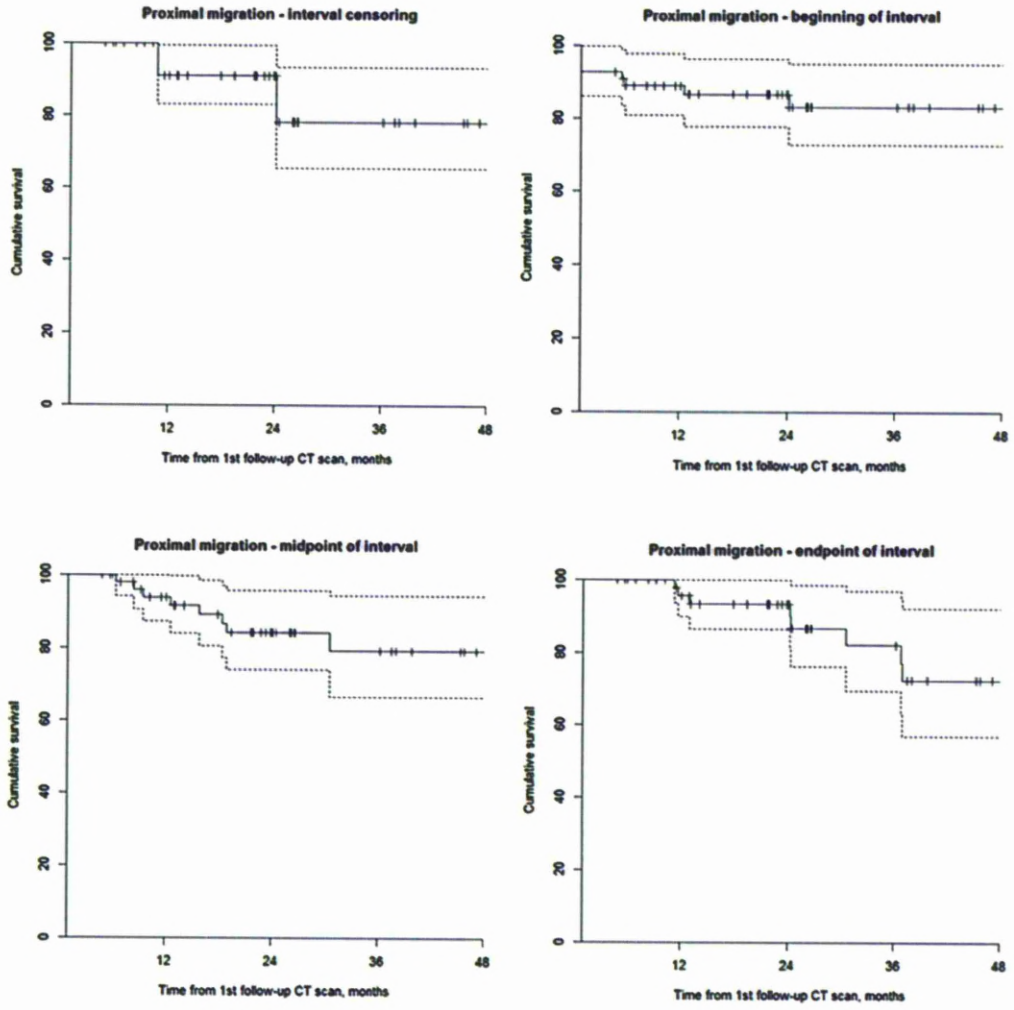
Table 5.4 Comparison of survival estimates (Kaplan-Meier) between the four approaches considered for proximal stent-graft migration. Percentages relate to the proportion of patients free from migration.

	Interval censoring			Beginning of interval		
Time, mo	**n. risk**	**survival**	**95% CI**	**n. risk**	**survival**	**95% CI**
12	42	91%	83% to 100%	40	89%	81% to 98%
24	29	91%	83% to 100%	26	87%	78% to 96%
36	16	78%	66% to 93%	16	83%	73% to 95%
48	9	78%	66% to 93%	9	83%	73% to 95%

	Midpoint of interval			End of interval		
Time, mo	**n. risk**	**survival**	**95% CI**	**n. risk**	**survival**	**95% CI**
12	43	94%	88% to 100%	44	96%	90% to 100%
24	26	84%	74% to 96%	30	93%	87% to 100%
36	16	79%	67% to 95%	18	82%	70% to 97%
48	9	79%	67% to 95%	9	73%	57% to 92%

Mo, months. n, number of patients. CI, confidence interval.

Figure 5.7 Kaplan-Meier survival curves illustrating freedom from proximal stent-graft migration using a combination of event time definitions. Percentage values across the y-axis relate to the proportion of patients free from migration. Corresponding 95% confidence intervals are represented by the outer (dotted) lines.



For those patients with CT evidence of proximal migration (n=10), 2 patients (20%) had device migration identified on the last follow-up CT scan. For the remaining eight patients there were only minor amounts of additional migration (mean +0.5 SD 0.8 mm)

during the remaining follow-up (mean 36 SD 15 months). Graft-related events and re-interventions are described in Table 5.5.

Table 5.5 Outcomes of patients with CT evidence of proximal stent graft migration

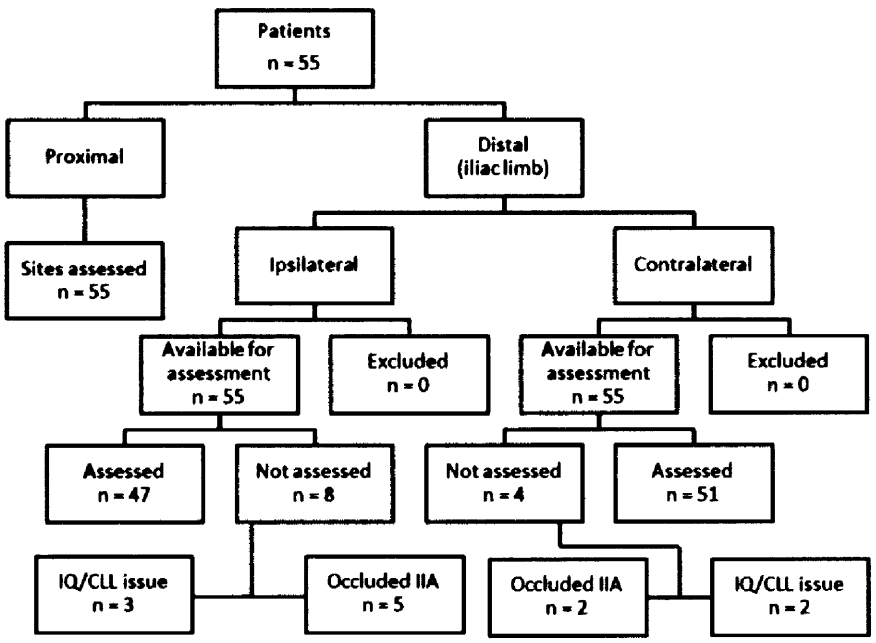
Patient	*Time to migration (months)*	*Migration distance (mm)*	*Pre-Op AAA diameter (mm)*	*Latest AAA diameter (mm)*	*Change in AAA diameter (mm)*	*Endoleak*	*TV event*	*Component Separation*	*Outcome*
1	36.9	+8.0	59	40	-19	No	LRA stenosis (Bridge Assurant, uncovered)	No	LRA stenosis on 1st post-operative CT. Alive at LFU (8 years), renal function stable, no reinterventions.
2	36.8	+7.4	70	39	-31	Type II	No	No	Clinical sequelae/reintervention free at LFU (5 years). Died - NARC.
3	24.3	+6.2	80	46	-34	No	No	No	Clinical sequelae/ reintervention free at LFU (6 years). Died - NARC.
4	84.7	+6.2	69	87	+18	Type II	No	Yes	Modular distraction of the main body. Bridging stent-graft was implanted at 36 months. No further complications/ reintervention. Patient alive at LFU (9 years).
5	24.2	+5.3	63	35	-28	Type II	SMA stenosis (unstented scallop)	No	Clinical sequelae/reintervention free at LFU (8 years). Died - NARC.
6	30.5	+5.0	58	59	+1	No	LRA occlusion (Jostent, covered)	No	LRA lost on 2 year CT. Migration reported 6 months later. Serum creatinine rose from 93 to 134 μmol/L during follow-up. No reintervention. Patient withdrew from follow-up after 5 years, died - NARC.
7	11.3	+4.7	59	57	-2	No	LRA occlusion (Advanta V12, covered)	No	Minor renal artery stenosis and calcification on pre-operative CT. LRA occlusion due to continuation of renovascular disease. Stable renal function, patient alive at LFU (2 years), no reintervention.
8	62.8	+4.1	78	70	-8	No	No	Yes	Modular distraction of the main body overlap at 4 years. Distraction led to kinking of the contralateral limb and was treated with a wallstent. Patient alive and complication/further reintervention free at LFU (7 years).
9	11.7	+4.1	64	46	-18	No	SMA stenosis (Advanta V12, covered)	No	Alive/free from clinical sequelae/ reintervention at LFU (2 years).
10	13.0	+4.0	71	77	+6	Type II	No	No	Alive/ free from clinical sequelae/reintervention at LFU (2 years).

LRA - left renal artery; SMA - superior mesenteric artery. Changes in AAA diameter, negative values denote a reduction in AAA diameter whereas positive values highlight an increase. Target vessel stent data; Jostent, Jomed International, Helsingborg, Sweden; Advanta V12, Atrium, Hudson, NH; Bridge Assurant, Medtronic, Santa Rosa, CA). NARC – non-aneurysm related cause.

Distal iliac limb migration

Using data from 55 patients, a total of 98 iliac limbs were assessed for the presence of distal migration. In eleven patients (12 CIA) a CLL was unable to be constructed, this was either due to a previously occluded internal iliac artery (n=7) or there were image quality issues (n=5) preventing the computer from generating a CLL e.g. poor contrast opacification. Further details on the inclusions and exclusions regarding the assessment of iliac limb migration are illustrated in Figure 5.8.

Figure 5.8 Iliac limb inclusions and exclusions (single centre cohort)



IIA, internal iliac artery; IQ, image quality; CLL, central luminal line.

Of the 98 iliac limbs assessed, 10 (10%) showed CT evidence of device migration, all were cranial in direction. Median distal migration was -5.0 (IQR, -8.5 to -4.4; range, -21.3 to -4.3) mm. The frequency and timings of iliac limb migrations, both ipsilateral and

contralateral, are described using a histogram in Figure 5.9 and Figure 5.10. Based on iliac limb follow-up of 124.1 person-years, this study identified a distal migration rate of 1 migration per 14 person-years of follow-up. For those patients with CT evidence of distal (iliac) migration, three out of 10 limbs (30%) were identified as migrated at last follow-up. For the remaining seven, there was only evidence of a small amount of further migration (mean -1.6 ± 1.4 mm) over a mean 27 ± 1 months.

Figure 5.9 Frequencies of distal (iliac) limb migration. In the two cases of iliac limb migration <-9 mm, one case (contralateral) had -10.6 mm and the second case (ipsilateral) had -21.3 mm of cranial migration

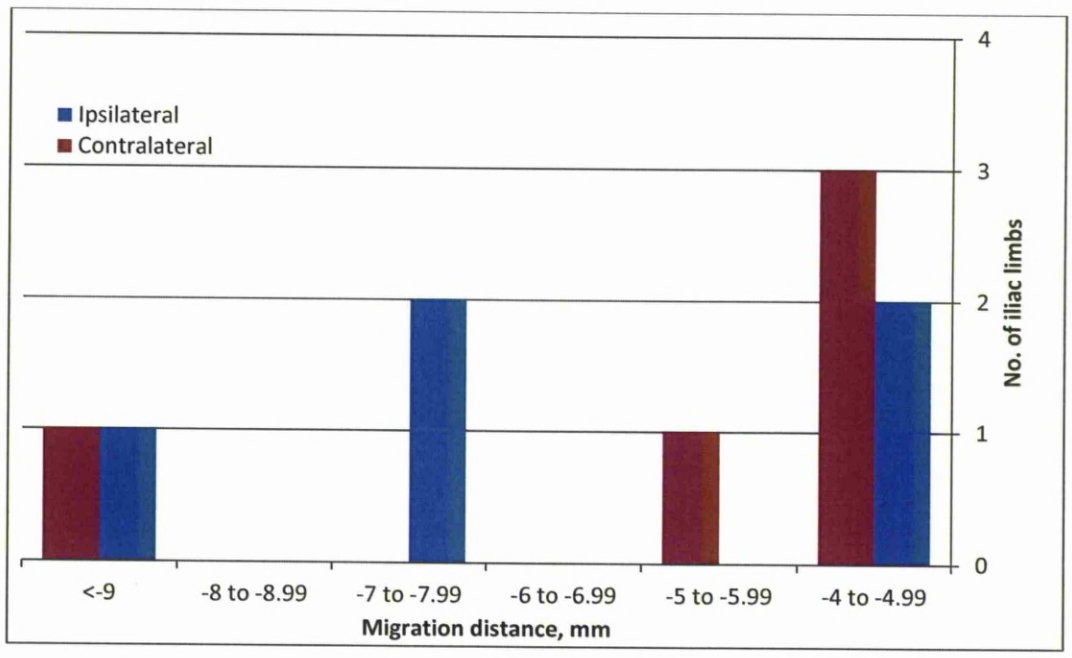
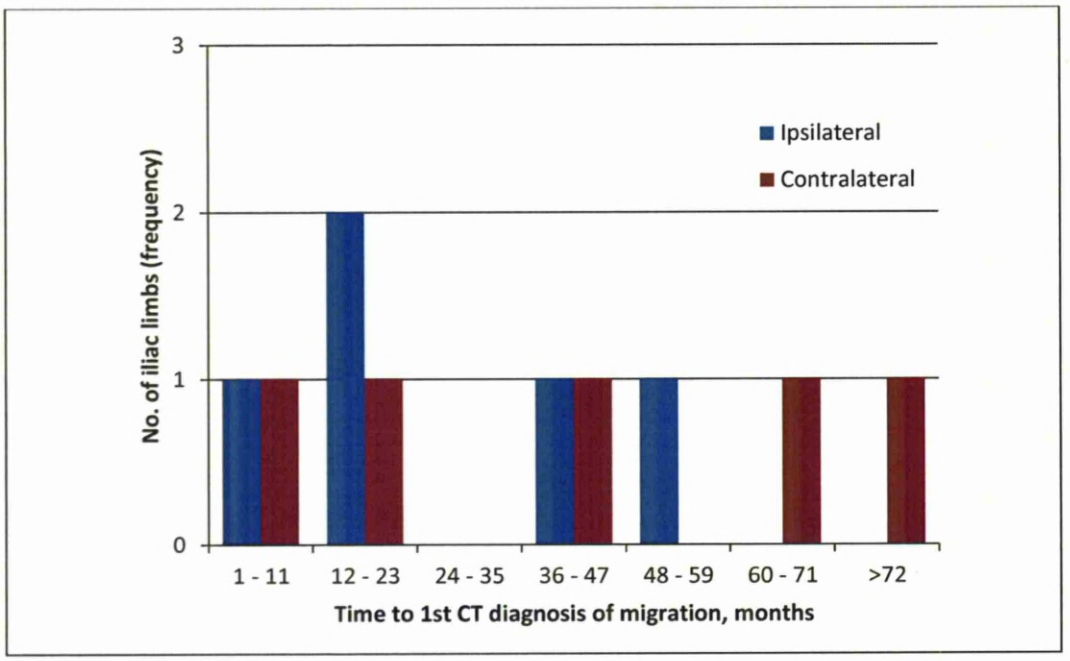


Figure 5.10 Time to 1st CT diagnosis of distal (iliac) limb migration



Kaplan-Meier survival analysis indicated that the probabilities of a patient being free from any iliac limb migration at 12 and 36 months were 95% (95% CI 89% to 100%) and 86% (95% CI 76% to 97%) respectively (Figure 5.11, Table 5.6). Analysis on an individual iliac limb basis estimated that the probabilities of being free from iliac limb migration, at 12 and 36 months, were 96% (95%CI 91% to 100%) and 89% (95% CI 78% to 100%) for ipsilateral and 98% (95%CI 93% to 100%) and 89% (95%CI 73% to 100%) for contralateral limbs, respectively (Table 5.7, Figure 5.12, Figure 5.13). Complications in patients with distal iliac migration are summarised in Table 5.8.

Table 5.6 *Comparison of survival estimates (Kaplan-Meier) between the four approaches for any iliac limb migration. Percentages refer to the proportion of patients free from any iliac limb migration.*

	Interval censoring			Beginning of interval		
Time, mo	**n. risk**	**survival**	**95% CI**	**n. risk**	**survival**	**95% CI**
12	40	95%	89% to 100%	37	89%	80% to 98%
24	25	86%	76% to 97%	24	86%	77% to 96%
36	17	86%	76% to 97%	16	86%	77% to 96%
48	11	70%	53% to 91%	11	75%	61% to 94%

	Midpoint of interval			End of interval		
Time, mo	**n. risk**	**survival**	**95% CI**	**n. risk**	**survival**	**95% CI**
12	40	94%	88% to 100%	41	96%	91% to 100%
24	24	83%	71% to 96%	27	90%	82% to 100%
36	16	83%	71% to 96%	18	86%	74% to 99%
48	11	71%	55% to 92%	12	69%	52% to 92%

Mo, months. n, number of patients. CI, confidence interval.

Figure 5.11 Kaplan-Meier survival curves illustrating freedom from any iliac limb migration using a combination of event time definitions. Percentage values across the y-axis relate to the proportion of patients free from migration. Corresponding 95% confidence intervals are represented by the outer (dotted) lines.

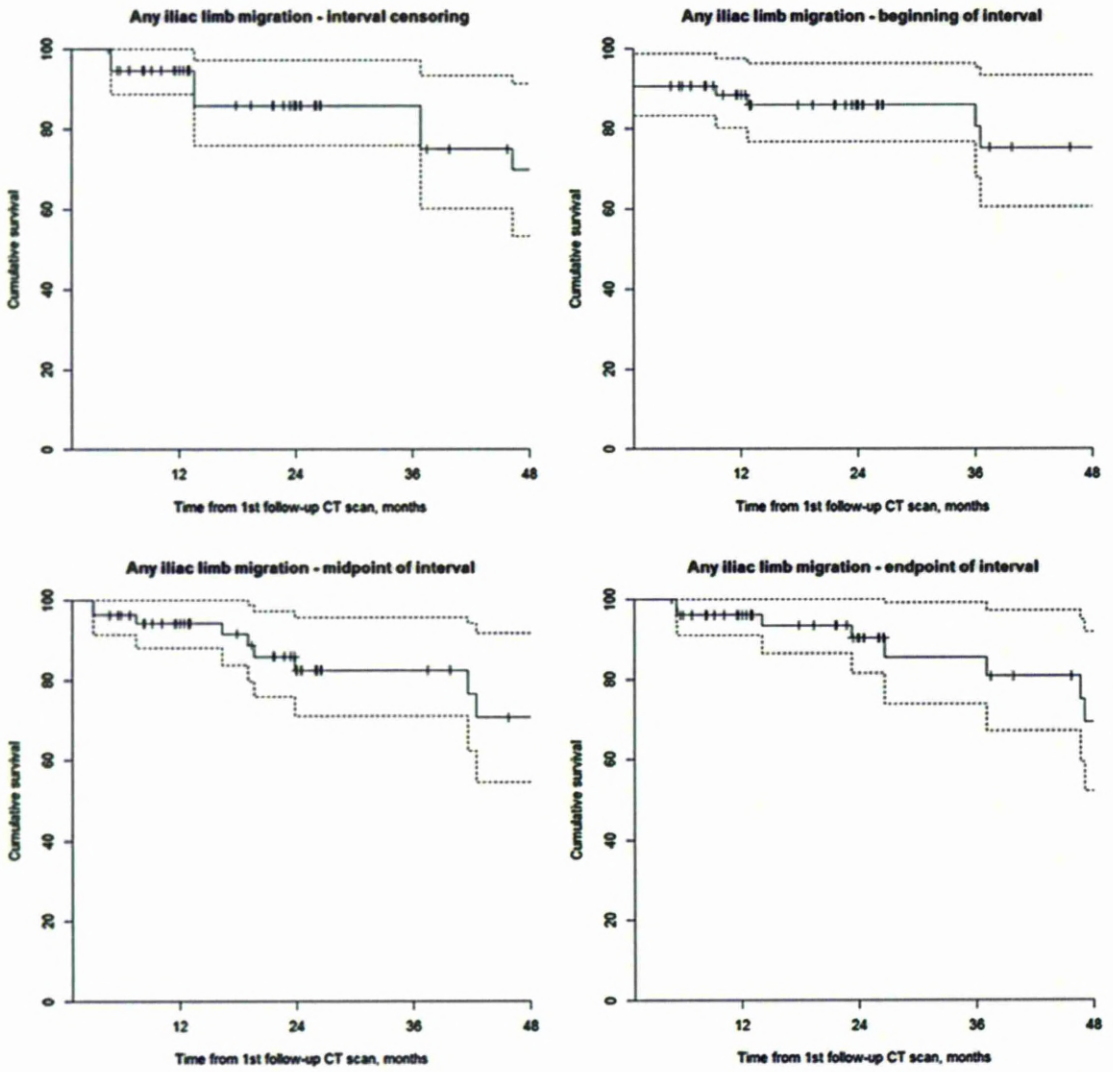


Figure 5.12 Kaplan-Meier survival curves illustrating freedom from iliac limb migration (Ipsilateral limbs only) using a combination of event time definitions. Percentage values across the y-axis relate to the proportion of iliac limbs free from migration. Corresponding 95% confidence intervals are represented by the outer (dotted) lines.

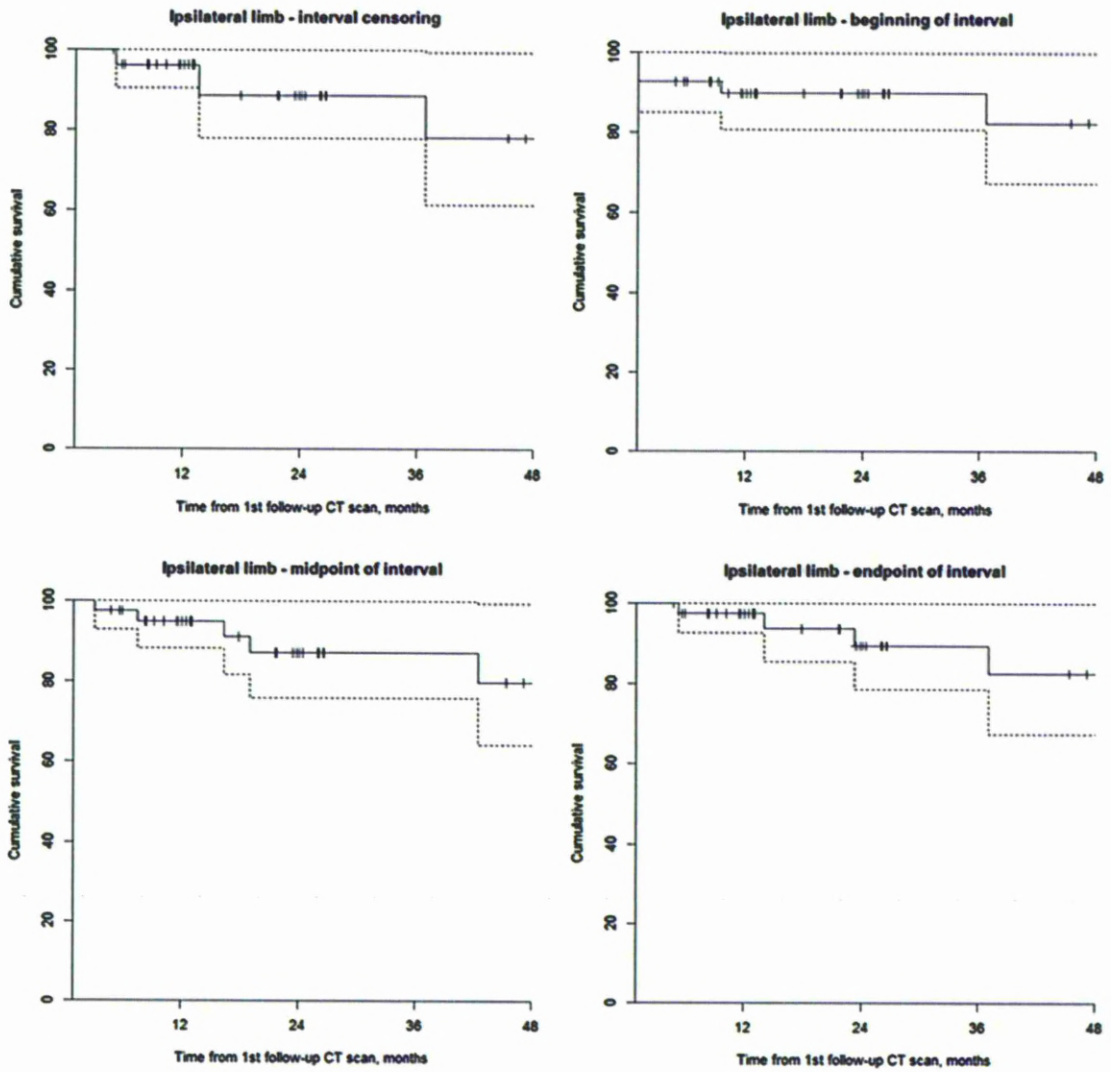
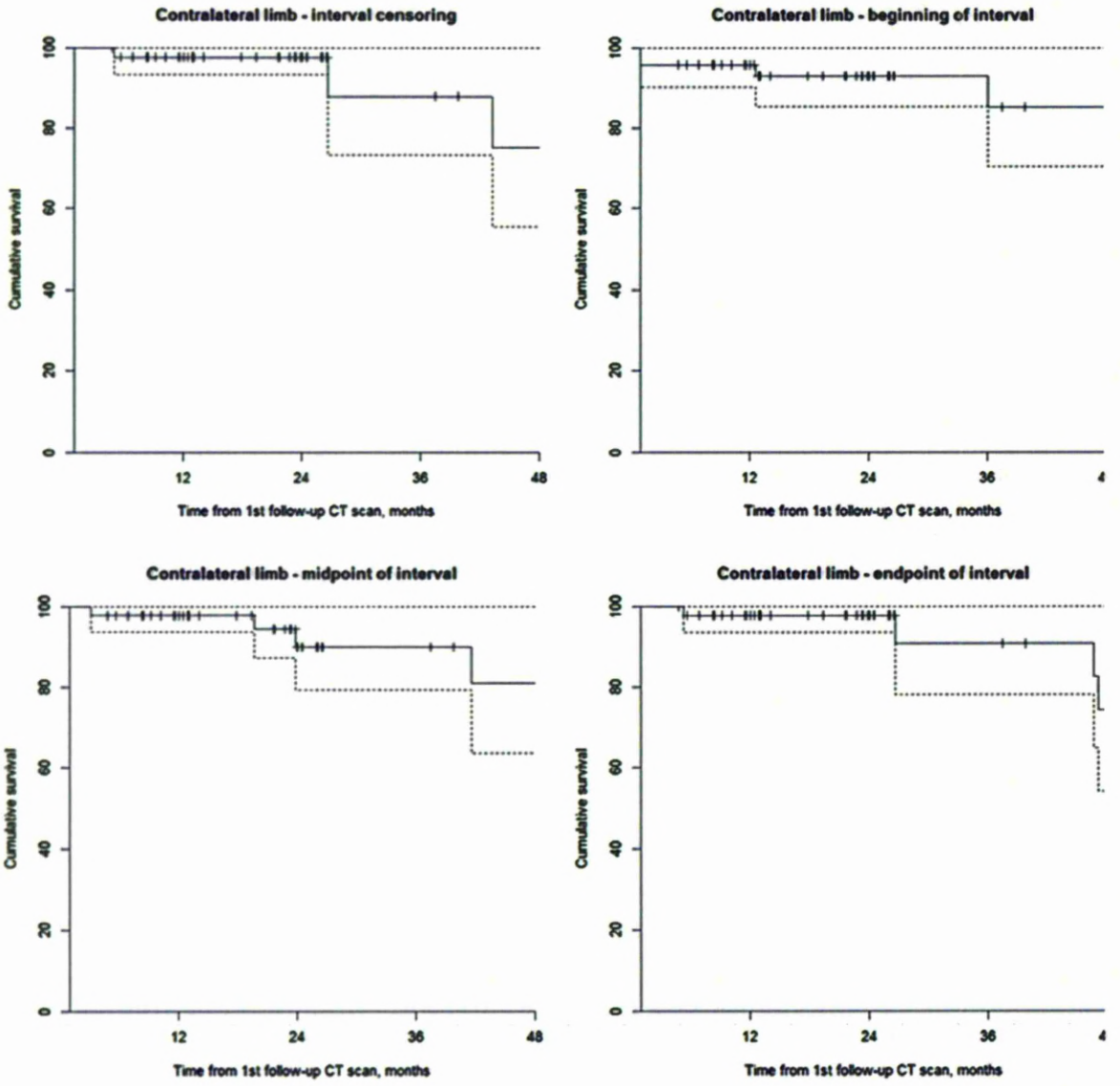


Figure 5.13 Kaplan-Meier survival curves illustrating freedom from iliac limb migration (Contralateral limbs only) using a combination of event time definitions. Percentage values across the y-axis relate to the proportion of iliac limbs free from migration. Corresponding 95% confidence intervals are represented by the outer (dotted) lines.



Upon visual inspection of Figures 5.13 and 5.14 suggested that there were no apparent differences between iliac limb types.

Table 5.7 Survival estimates (Kaplan-Meier) for the four approaches for iliac limb migration. Percentage values relate to the proportion of iliac limbs free from migration.

Ipsilateral	Interval censoring			Beginning of interval		
Time, mo	n. risk	survival	95% CI	n. risk	survival	95% CI
12	31	96%	91% to 100%	28	90%	81% to 100%
24	19	89%	78% to 100%	18	90%	81% to 100%
36	13	89%	78% to 100%	12	90%	81% to 100%
48	9	78%	61% to 99%	9	82%	67% to 100%

	Midpoint of interval			End of interval		
Time, mo	n. risk	Survival	95% CI	n. risk	survival	95% CI
12	30	95%	88% to 100%	31	98%	92% to 100%
24	18	87%	76% to 100%	19	90%	79% to 100%
36	12	87%	76% to 100%	13	90%	79% to 100%
48	8	80%	64% to 100%	10	83%	67% to 100%

Contralateral	Interval censoring			Beginning of interval		
Time, mo	n. risk	survival	95% CI	n. risk	survival	95% CI
12	37	98	93% to 100%	36	96%	90% to 100%
24	22	98	93% to 100%	20	93%	85% to 100%
36	13	89	73% to 100%	12	93%	85% to 100%
48	9	75	55% to 100%	9	85%	70% to 100%

	Midpoint of interval			End of interval		
Time, mo	n. risk	survival	95% CI	n. risk	Survival	95% CI
12	37	98%	94% to 100%	37	98%	94% to 100%
24	20	90%	79% to 100%	22	98%	94% to 100%
36	12	90%	79% to 100%	13	91%	78% to 100%
48	9	81%	64% to 100%	9	74%	54% to 100%

Mo, months. n, number of patients. CI, confidence interval.

Table 5.8 Outcomes of patients with CT evidence of iliac limb migration

Case	Limb	Time to migration (months)	Migration distance (mm)	Pre-Op AAA diameter (mm)	Latest AAA diameter (mm)	Changes in AAA diameter (mm)	Endoleak	Iliac reintervention	Outcome
1 (8)	Ipsi	37.1	-21.3	78	70	-8	No	No	Alive at LFU (7 years) – see proximal patient 8. No IRSI.
2	Contra	5.3	-10.6	70	61	-9	No	No	Alive at LFU (4 years), no complications/reinterventions.
3 (5)	Ipsi	48.4	-7.7	63	35	-28	No	No	Died – NARC (8 years) – see proximal patient 5. No IRSI.
4	Contra	5.4	-7.5	58	53	-5	Type II	No	Alive at LFU (3 years), no complications/reinterventions.
5	Contra	23.9	-5.0	57	60	+3	No	No	4 year follow-up, died - NARC. No complications/reinterventions.
6	Ipsi	12.2	-4.9	74	68	-6	No	No	Alive at LFU (3 years), no complications/reinterventions.
7 (8)	Contra	62.8	-4.6	78	70	-8	No	No	Alive at LFU (7 years) – see proximal patient 8. No IRSI.
8 (4)	Ipsi	89.5	-4.4	69	87	+18	No	No	Alive at LFU (9 years) – see proximal patient 4. No IRSI.
9	Contra	38.0	-4.4	85	86	+1	Type II	No	Alive at LFU (4 years), no complications/reinterventions.
10	Contra	23.3	-4.3	67	57	-10	Type II	No	2 years follow-up, died - NARC. No complications/reinterventions.

SMA - superior mesenteric artery; LRA - left renal artery; Ipsi – ipsilateral; Contra - contralateral. Changes in AAA diameter, negative values denote a reduction in AAA diameter whereas positive values highlight an increase. Numbers enclosed by the parentheses in the first column correspond to any related proximal migration cases in Table 3. NARC – non-aneurysm related cause; IRSI – iliac related secondary intervention.

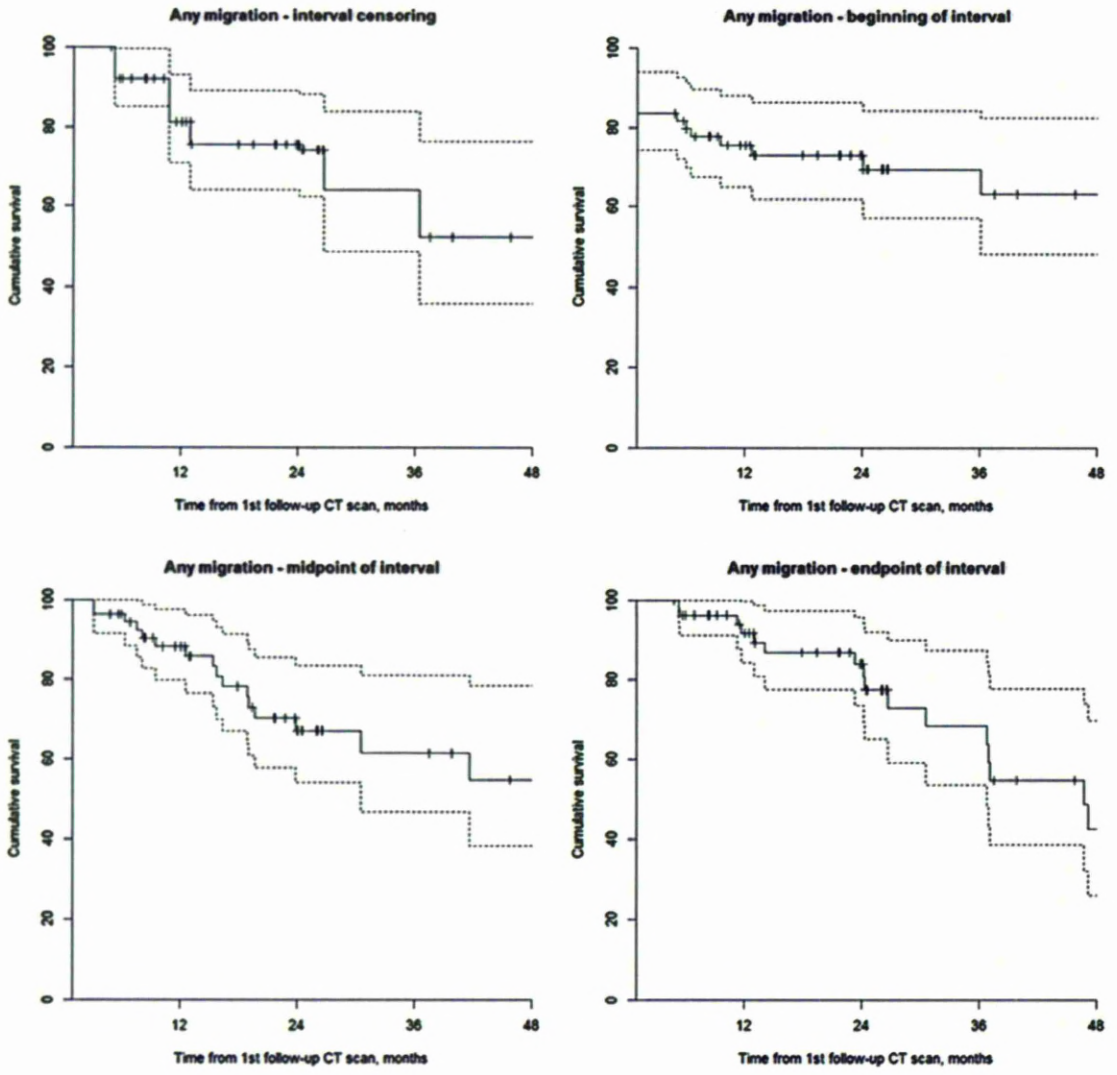
The concurrent migration of both iliac limbs was seen in one patient (2%). Migration at the proximal and at least one distal attachment site was seen in three patients (5%). Freedom from ***any*** (proximal or distal) migration at 12 and 36 months were 81% (95% CI 71% to 93%) and 64% (95%CI 49% to 94%) respectively (Table 5.9, Figure 5.14).

Table 5.9 Comparison of survival estimates (Kaplan-Meier) between the four approaches considered for any migration (proximal or distal). Percentage values relate to the proportion of patients free from migration.

	Interval censoring			Beginning of interval		
Time, mo	**n. risk**	**survival**	**95% CI**	**n. risk**	**survival**	**95% CI**
12	36	81%	71% to 93%	32	76%	65% to 88%
24	24	76%	64% to 89%	21	73%	62% to 86%
36	12	64%	49% to 94%	11	69%	57% to 84%
48	7	52%	36% to 76%	7	63%	48% to 83%
	Midpoint of interval			**End of interval**		
Time, mo	**n. risk**	**survival**	**95% CI**	**n. risk**	**survival**	**95% CI**
12	39	88%	80% to 98%	41	92%	84% to 100%
24	21	67%	54% to 83%	28	84%	74% to 96%
36	11	62%	47% to 81%	15	68%	54% to 87%
48	7	55%	38% to 78%	7	43%	26% to 70%

Mo, months. n, number of patients. CI, confidence interval.

Figure 5.14 Kaplan-Meier survival curves illustrating freedom from any device migration (proximal and/or distal). Percentage values across the y-axis relate to the proportion of patients free from any migration. Corresponding 95% confidence intervals are represented by the outer (dotted) lines.



5.4 Discussion

All commercially available infrarenal stent-grafts have had cases of stent-graft migration reported. Migration of these device can be serious and have been associated with complications including type I endoleak, rupture and open conversion. There is heightened concern regarding the migration of fenestrated stent-grafts. For these more complex devices, minor movements at the proximal margins of a device could be catastrophic and could result in visceral complications (e.g. mesenteric ischaemia, or the need for renal replacement therapy). For infrarenal stent-grafts there is a range in the reported incidence of migration. One hypothesis is that these are due differences in migration definitions and assessment methods. It has been further hypothesised that the assessment of more subtle levels of migration earlier could be advantageous and may even lower morbidity and mortality (Greenberg *et al.*, 2004b). CT techniques have been developed that now allow the quantification of more subtle levels of stent-graft migration. Up until now, these techniques have not been formally applied to a fenestrated cohort in order to allow the assessment of migration. Following the validation of the CT CLL migration measurement technique, this technique was successfully applied to a cohort of patients with fenestrated aortic stent-grafts implanted.

Data presented in this chapter represents the first single centre quantification of fenestrated stent-graft migration. From this 9% of patients had an estimated probability of proximal migration (≥4 mm) at 12 months. By 36 months, this had increased to 22% and by 48 months, it had remained at 22%. Iliac limb migrations were initially less frequent with 12 and 36 month probabilities of 5% and 14%, respectively. By 48 months the incidence of iliac limb migration had increased to 30%. Two key aims of this chapter were to report the

incidence and timings of migration. In doing so, it was important to compare these values against those reported within the literature. This was difficult since most reports were single centre efficacy studies, which documented short and mid-term outcomes and had very few references to device migration. There are, however, cases of proximal migration reported within these series (O'Neill *et al.*, 2006a, Ziegler *et al.*, 2007, Scurr *et al.*, 2008a, Verhoeven *et al.*, 2010, Greenberg *et al.*, 2009b, Troisi *et al.*, 2011). Comparison with these reports are limited, this is because there are a range of migration definitions and assessment techniques used. In the majority of cases, migration was only defined where there was a related clinical event or where reintervention was required. Based on this *'clinically significant'* definition the reported incidence within the literature ranges from 1% (O'Neill *et al.*, 2006a) to 12% (BSET and GLOBALSTAR Collaborators, 2012). Troisi and colleagues reported a higher (24%) migration rate, all of which required reintervention (Troisi *et al.*, 2011). The report by Troisi et al., was based on a mix of branched, fenestrated and combined branched/fenestrated devices and highlighted only cases of migration with a concurrent type I endoleak. In their series, there were an additional eight cases of in-stent stenosis or occlusion. It was not clear if stent-graft migration could have accounted for any of these events. It was also difficult to separate out those cases, which resulted solely from the migration a fenestrated stent-graft. There is, however, one advantage of comparisons with the current reports in the literature; all refer to the migration of the Zenith fenestrated AAA endograft which was the focus of this thesis. If this thesis adopted a similar (*clinically significant*) classification then the single centre migration rate would be 9%; two patients lost a single target vessel loss (both RAs) and three patients had stenosis of a target vessel (2 SMAs, 1 RA). Overall, the reported

incidence of proximal migration, based on the single centre experience reported in this chapter, is in keeping with rates published within the literature (Table 2.4).

With respect to the timings of proximal migration, there are very few comparative references with the literature. To the author's knowledge there are only three publications that have reported the timings of cases of fenestrated stent-graft migration. An efficacy series, in 2010, by Verhoeven and colleagues highlighted a single case of migration occurring at 24 months following implantation (Verhoeven *et al.*, 2010). The more recent German series by Troisi *et al.*, reported a series of migration-related reinterventions (n=8) in patients with an accompanying type I endoleak (Troisi *et al.*, 2011). In this report the timings of migration ranged from 4 to 68 months, however, interpretation these data must be taken with caution. Nicola Trosi and her research group reported only the timings of the reintervention and not the time of first diagnosis of migration. All cases had an accompanying type I endoleak and, therefore, these migrations were *clinically significant* and different from the definition used in this thesis. Troisi also made little comment on their migration assessment techniques. Their work is important as it does provide some indication of the event times for stent-graft migration. The most recent report documenting timings of migration (using Kaplan-Meier methods) was the report from the UK GLOBALSTAR registry. Freedom from proximal migration was reported as 99%, 92% and 88% at 12, 24 and 36 months, respectively (BSET and GLOBALSTAR Collaborators, 2012). Again the assessment techniques and definitions were not clearly defined and the overall follow-up of the study cohort was short (median 6 months). As such comparisons of proximal migration timings against those reported in the literature are difficult. The opinion of this thesis, taking into account the two relevant publications (Troisi et al., 2011, Verhoeven et al., 2010), is that

proximal migration of a fenestrated stent-graft can occur at any point during follow-up. There are likely to be various aetiologies which can explain migration at different time points. A discussion of these possibilities will be provided in the multicentre migration chapter (Chapter 6), where there is greater certainty around the incidence and timings of migration.

One methodological consideration, when considering the timings of migration, were the event time definitions used. Migration is a progressive event, if a numerical definition is used then the event will typically occur between two adjacent CT scans. Depending on how the migration time was defined will impact on the reporting of stent-graft migration. In this thesis four migration event time definitions were tested, these spanned across both the proximal and distal iliac landing zones. If it can be accepted that a more sophisticated interval censoring approach is superior, then the following trends can be observed. Using the beginning of the interval as the event time will overestimate the incidence of migration at early follow-up times e.g. 12 months. Conversely, using the end of the interval will cause an underestimation of the incidence but this trend was reversed for later follow-up times e.g. at 36 or 48 months. The closest approximation to interval censoring was when using the midpoint (the time halfway between the 1st CT scan where the migration was diagnosed and the previous CT scan) as the event time definition. It is surprising that the majority of research articles cited within this thesis did not contain information on any event time definitions used to report migration.

A further consideration within this chapter was the incidence and type of migration-related sequelae. Only two cases of target vessel loss were identified in patients with proximal migration. There are numerous reasons for the compromise of a target vessel, these can include the fabric shuttering from migration but there can be others. It is also

important to highlight that there were no cases of proximal type I endoleak, rupture or conversion to open repair in the cohort presented in this chapter. All three of these complications have been associated with migration of infrarenal stent-grafts (Wyss *et al.*, 2010, Harris *et al.*, 2000). Questions must arise regarding the absence of these complications, especially in view of proximal migration being identified in ten patients (20%). Various reasons can be suggested for this and there will be a further more detailed discussion within the multicentre chapter. With respect to this single centre cohort, both the sample size and duration of follow-up could be attributed to the lack of ruptures and open conversions. There are also major differences in the stent-graft design between those used in this chapter (fenestrated) and those where migration-related ruptures have been reported (infrarenal). The assessment and classification of more subtle levels of migration will also affect the relationship with serious sequelae. If the migration definition was more liberal (i.e. ≥ 10 mm) then there would have been a lower incidence and fewer patients would have been expected to have migration-related sequelae. Excluded patients must also be a consideration. Could any exclusions be the result of migration or a migration-related sequelae? Within this chapter the bulk of the exclusions were due to a lack of CT data and not losses to follow-up. The exception would be cases that were followed up externally. The ethical approval process (single centre) did not permit access to external follow-up CT data or allow the ascertainment of the follow-up status of patients outside of the treating institution (single centre). In the UK, FEVAR practice spans across a small number of centres, as a result outcome data and experience is constantly been sought in order to inform practice and satisfy funders. If there were ruptures or significant complications at external centres then it is likely that they would have been communicated back to the treatment hospital. At the

time of writing, there have been no such reports made to Hospital A regarding any of the single centre data presented.

With regard the two cases of renal artery occlusion, both were deemed not to result from proximal migration. Patient 6 had widely patent and stenosis free renal arteries on both preoperative and 1st postoperative CTA. A left renal artery occlusion was reported at 2 years, it was a further six months before the device migration reached a detectable threshold (≥4 mm). Analysis of follow-up imaging (CT and abdominal radiographs) demonstrated no evidence of stent crushing or fracture. Following occlusion, the patient's serum creatinine levels rose from 94 to 134 μmol/L, without any need for dialysis. Due to the presence of significant comorbidities the patient withdrew from follow-up at 5 years and has since died from a non-aneurysm related cause. Patient 7 also had a left renal artery occlusion detected at 2 years, 12 months after the initial diagnosis of proximal migration. During follow-up, the CT and ultrasound examinations continually demonstrated a reduction in left renal artery blood flow and associated left renal atrophy. On preoperative imaging the patient had a minor stenosis with some calcification of the left renal artery. The occlusion was, therefore, felt to be the result of a continuation of the patient's renovascular disease. Renal function has remained stable with serum creatinine levels around 100 μmol/L and the patient was alive and well at last follow-up, 2 years. Stent-graft migration with resultant shuttering of the fabric over the ostium of the vessel is a possible cause of target vessel loss. Other factors include the misalignment of a fenestration during deployment, pre-operative quality of the target vessel, progression of atherosclerosis, distal embolisation and intimal hyperplasia.

A further consideration is the magnitude of proximal migrations alongside event times. The majority of proximal migrations were caudal movements of less than 6 mm (60%). Based on KM survival analysis with interval censoring, review of the time to 1st CT diagnosis of proximal migration histogram (Figure 5.6) and the proximal migration outcomes table (Table 5.5) it can be reported that proximal migration occurs at around 8% per year. Proximal migration also appears to be most frequent within the first 25 months following implantation. Both the early peak and size of movements may suggest that the majority of movements are the result of barb engagement. This theory of an initial phase of stent-graft movement, which was associated with barb engagement, has been reported in a lab based study (Zhou *et al.*, 2007). A full and more detailed evaluation of the causative factors for proximal migration will form part of the discussion in the next two chapters (multicentre data and predictive factors).

With respect to iliac limb migration, 10% of distal iliac limbs migrated during follow-up and all were cranial in direction. Distal iliac limb migrations appear to be more of a late occurring event with a peak between years 3 and 4 with an annual migration rate of 8%. The range of distal migrations (-4.3 mm to -21.3 mm) was larger than proximal migration and may reflect the absence additional fixation mechanisms (e.g. barbs and target vessel stents). Similar to proximal migration, there is also a general absence of published data on the incidence and timings of distal stent-graft migration. Three series were identified from the literature, two were case reports but all used devices other than a Zenith fenestrated AAA stent-graft. In the first, cranial limb migration occurred at around 4 years with an associated type I endoleak and aneurysm expansion (Maleux *et al.*, 2001). The migration caused severe kinking of the limb, an endovascular solution was not possible and the patient received an

open conversion. The second was a case of bilateral iliac limb migration at 5 years with an accompanying distal type I endoleak (Alerci *et al.*, 2005). This patient was successfully treated with an endovascular solution. The third report was from the US Vanguard endograft trial investigators (Beebe *et al.*, 2001). Distal iliac limb migration was observed in two patients (0.7%); both were at 12 months following repair and were successfully treated using an endovascular approach. Comparison with the study by Beebe *et al.*, is limited. The Vanguard device is a 1st generation stent-graft and is no longer commercially available. In addition, there were no formal mechanisms for assessing distal iliac limb migration within the study methods. The report was published in 2001, thin-slice MDCT technology was not widely available and most vascular CT examinations relied on ≥ 5 mm CT slices. Such CT data would have undoubtedly caused problems if the investigators had attempted to assess subtle stent-graft migration.

Data within this chapter suggests that there are no differences in migration rates between limb types (ipsi- and contralateral). Migrations were almost equally distributed between ipsilateral (n=4) and contralateral (n=6) limbs. Related-sequelae for distal migration were also favourable. There were no cases of distal type I endoleaks irrespective of the presence of migration within data reported in this chapter. Iliac limb occlusions are also a possibility but no late limb losses were reported in this cohort in patients with either proximal or distal stent-graft migration.

Limitations

In reporting data in this chapter it is accepted that there are limitations. Thirty-four per cent of the initial cohort were excluded, this was primarily due to a lack of available follow-up CT scans. In Hospital A (single centre) PACS was introduced in 2006, prior to this time it was difficult to gain retrospective access to CT data. Ten per cent of patients had follow-up at another institution and whilst it may have been possible to locate their CT data, this would have been outside of the ethics approval. The issue of whether some of these patients were excluded because of migration or migration-related sequelae has been previously discussed. There are also limitations in the reporting of distal iliac limb migration. There were several instances when a CLL migration measurement could not be obtained. This was either due to CT image quality issues or the absence of a clearly visible CIA bifurcation due to prior IIA occlusion or procedural embolization and graft extension into the EIA. It is important to understand that in eleven cases, a deployed iliac limb was present and migration assessment was not possible. These limbs could have undergone migration and as such interpretation of the iliac limb migration rates reported must consider this factor. A sensitivity analysis has been undertaken in the multicentre chapter, this will help understand the possible effects of missing CLL measurements when reporting iliac limb migration.

It was technically possible to statistically compare the complication and reintervention rates between patients with and without stent-graft migration. Due to the small number of migrations, complications and reinterventions these have described only using summary statistics. All full analysis, including appropriate statistical testing, will form part of the next (multicentre) chapter.

5.5 Conclusion

Migration of a fenestrated stent-graft is potentially catastrophic but can be effectively assessed using a CT central luminal line technique. Based on a single centre sample of fifty-five patients, migration at the proximal and distal landing zones occurs in around a quarter of patients by four years. The bulk of the migrations are less than six millimetres in length but movements of greater than ten millimetres are possible at both landing zones. Despite this observation, migration appears to take a relatively benign course. In order to have a greater understanding of this phenomenon, further analysis of a larger number of patients and migration events are required.

6. Fenestrated Stent-Graft Migration: a multicentre analysis

6.1 Introduction

There have been little multicentre outcome data for patients treated by FEVAR. Data from a single systematic review (Sun *et al.*, 2006), a small (30 patients) US prospective trial (Greenberg *et al.*, 2009a), a retrospective French multicentre (134 patients) series (Amiot *et al.*, 2010) and more recently the UK GLOBALSTAR registry (BSET and GLOBALSTAR Collaborators, 2012) have been published. Generating multicentre data can bring many advantages, these include the ability to recruit a larger numbers of participants, across different geographical locations and the ability to compare results between centres (Waldron and Cookson, 1993). Such advantages have also been said to increase the generalizability of the resultant study findings (Guthrie *et al.*, 2012). Within this context, Hughes and Watkins (2012) recently highlighted the need to acquire multicentre data in order to answer questions of complex endovascular repair. Endovascular techniques are often considered to be a substantial way behind open surgery, when it comes to the reporting of procedural outcomes data and trend analysis. As an example, a multicentre analysis of complex open aortic aneurysm repair from the National Surgical Quality Improvement Program (NSQIP) database analysed data from nearly 600 patients (Khuri *et al.*, 1998). Such large multicentre series do not exist for FEVAR. In the UK the GLOBALSTAR registry is the largest collection of multicentre FEVAR outcomes and includes retrospective data from over 300 patients across 14 UK centres (BSET and GLOBALSTAR Collaborators, 2012). For the investigation of fenestrated stent-graft migration, there are no directly focused studies, either single or multicentre that have reported within the literature.

The recent report from the UK GLOBALSTAR registry documented proximal fenestrated stent-graft migration rates of 8% and 12% at 24 and 36 months, respectively (BSET and GLOBALSTAR Collaborators, 2012). It was, however, not stated in the methods section how migration was assessed or any reporting standards used to define the complication. Further limitations of the GLOBALSTAR report are that median follow-up was only six months and that complications were assessed by the treating institution and not a core lab or independent review group. Other studies, which have highlighted cases of migration, have generally relied on subjective markers e.g. gross positional changes or have simply chosen only to report, cases where migration led to a clinical event, e.g. endoleak or where reintervention was required. Greenberg and colleagues have previously alerted the vascular community to the potential advantages from identifying migration early (Greenberg *et al.*, 2004b). To do this, would require more subtle detection methods and appropriate reporting standards.

FEVAR is both a relatively new procedure and technically complex. In the previous chapter, the migration rates for FEVAR patients treated at a single institution were reported. This provided essential information on the utility of the validated CLL technique when used to quantify fenestrated stent-graft migration. Experimental data from this chapter also provided early information on the incidences, timings and complications relating to fenestrated stent-graft migration. Using a larger sample size has allowed this thesis to provide greater certainty around the overall thesis aims.

Within the UK, both device manufacturers and government agencies, recommend lifelong imaging surveillance following stent-graft AAA repair (National Institute for Health and Care Excellence, 2006, Medtronic, 2012, Cook Medical, 2013). For a patient with a

fenestrated stent-graft implanted, the follow-up strategy usually includes contrast-enhanced CT scanning at 1-month, 6-months and then annually thereafter. As a result, there is a growing cohort of FEVAR patients across the UK, from which the position of the stent-graft can be tracked using these serial CT scans. The bulk of the FEVAR experience has been developed through a small number of specialist centres under the guidance from a single manufacturer. It is, therefore, highly likely that both the CT follow-up protocols and the implantation procedures will be similar between comparator institutions. However, heterogeneity in the migration rates between centres will be considered within this chapter.

6.1.1 Aims

Using multicentre CT data acquired for patients who have undergone fenestrated stent-graft repair the research aims for this chapter are to:-

Aim 6.1. Quantify the incidence of proximal and distal (iliac) stent-graft migration of the Zenith fenestrated AAA endograft;

Aim 6.2. Investigate the timings of proximal and distal (iliac) stent-graft migration;

Aim 6.3. Report the frequency and type of migration-related complications and secondary (reinterventional) procedures encountered in this cohort.

Data generated from this chapter has also been used as the basis for the predictive factor analysis which has been presented in Chapter 7.

6.2 Materials and methods

Within this chapter, several of the methods used to assess migration have been previously described. These are within previous chapters of this thesis and within the published

literature (England *et al.*, 2012, England *et al.*, 2013). In summary, this was a multicentre retrospective review of follow-up CT data in patients who had fenestrated aortic stent-grafts implanted within the United Kingdom.

6.2.1 Patients

Patients of both genders, who had a fenestrated aortic aneurysm repair, were considered for inclusion. Each patient needed to have had their AAA treated using a fenestrated aortic stent-graft (Zenith fenestrated AAA endograft, Cook Medical Inc, Bloomington, IN). Patients were identified from local endovascular databases and using the GLOBALSTAR registry. The GLOBALSTAR registry is a summary of UK FEVAR experience and recruited data from a total of 318 patients (14 centres). Inclusion into GLOBALSTAR was strict and required participating centres to have previous experience of both EVAR and FEVAR. Funding and project timescale restrictions would not allow a complete set of CT data to be obtained from all centres and for all patients included in GLOBALSTAR. Ethics approval (NRES 09/Q1502/43) and local Trust R&D approval permitted the inclusion of data from nine GLOBALSTAR participating hospitals. A single study researcher, who was the author of this thesis, was responsible for case recruitment, data collection, and follow-up analysis.

6.2.2 Sample size justification

Previous exploratory (pilot) work at Hospital A helped inform a sample size calculation. Based on linear regression, a sample of approximately 140 patients would be required to detect an annual migration of the stent-graft equal to 2mm/year against the null hypothesis "slope = 1mm/year" (regarded as the non-migration scenario). A significance level equal to 5% was considered together with study power equal to 90%. This calculation

was based on a sample standard deviation of migration equal to 2.6 mm. The standard deviation was based on a sample of 27 patients with fenestrated aortic stent-grafts implanted and an interval of follow-up of 24 months. This initial pilot work was undertaken prior to the validation experiment (Chapter 4). Data from the validation chapter has since highlighted the limitations of treating migration distances as a continuous variable. From the validation experiment, it was concluded that the quantification of stent-graft migration equal to or greater than 4 mm is possible using current follow-up CT protocols. Stent-graft movements of less than 4 mm cannot be accurately quantified and, therefore, linear regression using these more subtle movements (0 to 3.99 mm) are likely to be unreliable. This issue was not known about during the initial pilot work and could not be accounted for in the initial sample size calculation. In order to adjust for this within this this chapter and in the subsequent predictive factor analysis, migration will be treated as dichotomous (binary) variable using the ≥ 4 mm definition. It should be made clear that the primary reason for the sample size calculation was to consider the ability of the dataset to provide information on predictive factors. Studies using fewer patients (n=113) have successfully reported predictive factors for migration of standard (infrarenal) aortic stent-grafts (Cao *et al.*, 2002). In the study by Cao and colleagues, stent-graft migration was reported in only 15% of patients, this is a similar incidence to the single centre FEVAR experience in Chapter five of this thesis (18%). The report by Cao *et al.*, also treated migration as a dichotomous variable (definition, movement ≥ 10 mm). Bearing in mind both of these factors, it appears appropriate for the multicentre data to be analysed for predictive factors and this will be a feature of the next chapter. Based on the numbers of possible migration events the hypothesis to be tested will

be that the frequency of complications and reinterventions is indifferent between patients with evidence of proximal migration and those patients without.

6.2.3 Research procedures applied

The primary aims for this chapter are to report the incidence (Aim 6.1), the timings (Aim 6.2) and the related sequelae (Aim 6.3) for both proximal and distal migration of fenestrated aortic stent-graft. In order to satisfy each of the above aims the following data collection and analysis procedures were utilised.

In order to satisfy Aim 6.1 the incidence of stent-graft migration was reported for each of the three endograft attachment sites (proximal, ipsilateral and contralateral iliac limbs). All FEVAR patients had previously undergone follow-up to a standardised surveillance protocol (CTA preoperatively, at 1-month, 6-months and annually thereafter). Electronic copies of all available CT scans were collected, transferred and stored anonymously at the study institution. The availability of the CT scans varied through the participating centres. On the basis of the results in Chapter 4, any CT scan with a significant deviation from the protocol used in the validation experiment was excluded from the analysis. Examples are CT scans without adequate intraluminal contrast, which were excluded as they could give rise to an unreliable CLL. Such problems have been reported in a similar study by Wyss and colleagues and they also chose to exclude unsuitable CT scans from their analysis (Wyss *et al.*, 2011).

A thorough explanation of the precise methods used to quantify stent-graft migration has been described in chapters 4 and 5 (England *et al.*, 2012, England *et al.*, 2013). In summary, the 1st post-operative CT scan was used as a baseline in order to measure the

distance between the attachment sites and a vascular reference point. This measurement was then repeated on all available subsequent CT scans. Any measurement differences between the 1st postoperative CT scan and subsequent scans (of ≥ 4 mm) would be considered stent-graft migration. Movement of the stent-graft in a caudal direction was indicated by a plus sign (+) and movement in a cranial direction by a minus (-).

For Aim 6.2, the timings of device migration would initially be determined based on the date of the first CT scan when stent-graft migration was detected. The date of graft implantation would then be subtracted from this in order to give a migration time. For the majority of cases early stent-graft migration is likely to be asymptomatic. For these patients the exact time of migration (≥4 mm of movement) would be at a point between two serial CT scans e.g. 1st post-operative and 2nd post-operative. If these CT scans were performed at relatively close intervals e.g. monthly then this would generate a more precise estimation of the actual migration time. In reality, most patients with migration, the migration would be diagnosed between two annual CT scans (e.g Year 3 and Year 4). As previously stated, the reporting and estimation of migration rates must also take into account the time interval between serial follow-up examinations. Further details on the possible approaches to dealing with interval censoring survival data are described in the statistical section of Chapter 5. For this chapter the event time definitions will be the same, the beginning, the midpoint and the end of the interval together with an interval-censoring approach. These definitions will again be used to report survival data using Kaplan-Meier methods.

Aim 6.3 of this chapter was to report the association between device migration and any adverse complications or secondary interventions. The technique for identifying complications and reintervention was described in the previous chapter and was applied to

this multicentre cohort. Follow-up CT data, local endovascular databases and the GLOBALSTAR registry helped to establish the presence or absence of any complications or reinterventions.

6.2.4 Procedural reporting standards

When reporting migration data for the Zenith AAA endovascular stent-graft (Cook Inc, Bloomington, IN) it is important to provide key data on the patient sample and specific details around individual stent-graft configurations used. Reporting standards for endovascular repair do exist. The two most relevant standards are from the Society of Vascular Surgery (SVS) / International Cardiovascular Society (ICVS) (Chaikof *et al.*, 2002a) and clinical practice guidelines from the Society of Interventional Radiology, which are endorsed by the Cardiovascular and Interventional Radiological Society of Europe and the Canadian Interventional Radiology Association (Walker *et al.*, 2010). A more recent UK report, by Boyle and colleagues, will be used to assist in the description of the sample (Boyle *et al.*, 2011). It is necessary to report such variables, as it allows the generalisability of results against other FEVAR cohorts. The reporting of the FEVAR procedure and its outcomes has followed a similar structure to that of the previous chapter.

6.2.5 Statistical analysis

As with the previous chapter, all statistical analyses were undertaken using a combination of SPSS for Windows Version 21.0 (IBM Corp, Armonk, NY) and the statistical programming package R 2.2.1 (R Development Core Team, 2005). The multicentre data generated in this chapter were analysed in a similar manner to the data in Chapter 5. For full details of the statistical analyses please refer to the previous statistical analysis section. In addition, using

Kaplan-Meier survival analysis, a log-rank test (Fay and Shaw, 2010) was undertaken in order to compare freedom from proximal stent-graft migration in patients with and without evidence of complications or reinterventions. The use of a log-rank test was further developed to assess the differences between migrations rates for the single centre cohort (Hospital A) and the additional multicentre data (Hospitals B – I). Full details of this analysis are provided at the end of this chapter.

6.3 Results

6.3.1 Description of dataset

Patients treated by FEVAR from February 2003 through to March 2012 were entered into this retrospective review following entry into the GLOBALSTAR registry (n=154). Additional patients had undergone FEVAR but either failed to satisfy the study inclusion or satisfied the exclusion criteria. The most abundant reason for exclusion was a lack of a baseline (1st) post-operative CT. Reasons for this included imaging outside of the treating institution, absence of CT data on the hospital PACS or an inability to secure approval from the NHS site to receive CT data. Details of the study exclusions can be found in Table 6.1. When considering the total number of patients available within the GLOBALSTAR registry, this potentially included all patients treated by each of the respective institutions. It is, therefore, accepted that there may be a learning curve associated with some of the early patients included within this chapter. Based on an evaluation of selected parameters from the GLOBALSTAR database, there were no significant differences between the two groups (included and excluded). The median (IQR) age was 73.0 (68.0 to 78.5) years for included patients and 74.4 (69.3 to 80.0) years for excluded (P=0.12). Of the 154 patients included, 91% were men versus 89% in the excluded group (P=0.37). Similarly for AAA diameter, in the included group

the median (IQR) diameter was 62 (58 to 69) mm versus 60 (58 to 70) mm for the excluded group (P=0.92). It should be noted that a full range of preoperative variables (entry parameters) were not available for excluded patients and a comparison has been made based on those available.

Table 6.1 Summary of inclusions and exclusions from the participating centres (n refers to the number of patients)

		Included	
Clinical Site	**Total Cohort**	**n**	**%**
A	83	60	72%
D	44	14	32%
B	36	23	64%
F	23	12	52%
E	19	14	74%
C	19	16	84%
I	18	3	17%
G	14	8	57%
H	6	4	67%
	Total available cohort	262	
	Included, n	154	
	Included, %	59%	

Numbers of patients eligible for inclusion within this study (total available cohort) did include each individual centres learning curve (this is a requirement of inclusion in the GLOBALSTAR registry.

For the included patients, baseline demographics, comorbidities and American Society of Anesthesiologists (ASA) physical status gradings (Dripps, 1963) are described in Table 6.2. Variable selection was based on available data available from the UK GLOBALSTAR registry (BSET and GLOBALSTAR Collaborators, 2012), parameters routinely recorded in local

endovascular databases and those suggested by relevant reporting standards. It must be noted that this was largely a multicentre retrospective review and that the majority of variables were entered through a secure website. Some variables were not submitted for several patients and the degree of missingness, where present, has been described within each of the relevant results tables.

Table 6.2 Description of multicentre cohort (baseline demographics, comorbidities and AAA diameter)

Continuous variables

	Mean	SD	Median	IQR	Min.	Max.	Normality test	n	Missingness (%)
Age (years)	73.9	6.8	74.0	69.0 to 79.0	54.0	87.0	0.06	151	2%
Maximum aneurysm diameter (mm)	66.4	9.5	65.0	59.3 to 72.0	52.0	108	<0.001	152	1%

SD, standard deviation. IQR, inter-quartile range. Min, minimum. Max, maximum. Normality test, Shapiro-Wilk. Shaded areas indicate the appropriate summary statistic when considering the distribution of the data.

Categorical variables (n=154)

	n	n (%)	Missing	Missingness (%)
Gender				
Male	141	92%	0	0%
Ischaemic heart disease	64	42%	27	18%
Heart failure	9	6%	28	18%
Hypertension	84	55%	27	18%
Chronic renal insufficiency	10	7%	28	18%
ASA physical status grade				
I	1	1%		
II	32	21%		
III	76	49%	37	24%
IV	8	5%		
Diabetes mellitus	15	10%	27	18%

ASA, American Society of Anesthesiology. Definitions for categorical variables are provided within the appendices. n, number of patients.

6.3.2 Operative details (procedure)

Cook Zenith fenestrated stent-grafts were successfully implanted into all included patients. A variety of target vessel configurations were used (Table 6.3), the most common was an SMA scallop and two renal fenestrations. There were a total of 468 target vessels, of which 335 (72%) were stented (Table 6.3).

Table 6.3 Graft shape and target vessel configuration for the multicentre cohort

Categorical variables (n=154)	n	%	Missingness (%)
Graft shape			
Tube	6	4%	
Aorto-uni-iliac (AUI)	5	3%	0%
Bifurcated	143	93%	
Target vessel configuration			
CA			
Scallop (stented)	29 (0)	19% (0%)	0%
Fenestration (stented)	6 (6)	4% (4%)	
SMA			
Scallop (stented)	93 (0)	60% (0%)	0%
Fenestration (stented)	45 (44)	29% (29%)	
RT renal			
Scallop (stented)	7 (2)	5% (1%)	0%
Fenestration (stented)	137 (137)	89% (89%)	
LT renal			
Scallop (stented)	6 (2)	4% (1%)	0%
Fenestration (stented)	145 (144)	94% (94%)	

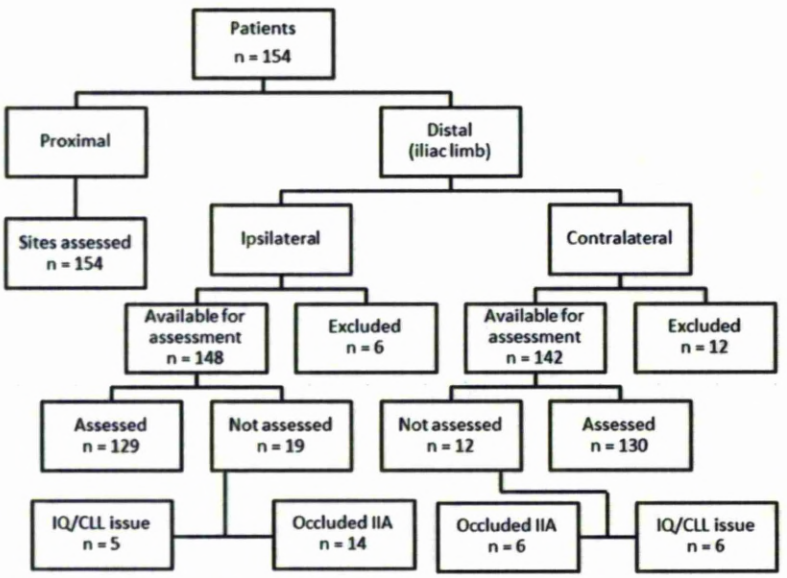
Under the section of target vessel configuration values in the parentheses indicate the number and percentage of stented vessels. CA, coeliac axis. SMA, superior mesenteric artery. RT, right. LT, left. n, number of patients.

All patients were followed-up according to local protocols within the respective study institution. Patients were followed-up for a median 20.9 (IQR 10.4 to 36.5, range 6 to 109) months.

6.3.3 Device migration

Based on the retrospective collection and analysis of 564 follow-up CT scans, the distance between the proximal and distal positions of the stent-graft (SMA to proximal stent and CIA bifurcation to distal stent) were measured and compared. Using previously acquired validation data (Chapter 4) the criteria for stent-graft migration was defined as any movement (proximally or distally) ≥ 4 mm. The presence of proximal stent-graft migration was assessed in a total of 154 patients and a subsequent assessment of iliac limb migration was possible in 259 CIAs. Full details on the landing sites assessed within the study cohort are illustrated in Figure 6.1.

Figure 6.1 Inclusions and exclusions within the multicentre cohort



IIA, internal iliac artery; IQ, image quality; CLL, central luminal line. Reasons for exclusion include tube and aorto-uni-iliac device with an absent iliac limb.

Proximal migration

Thirty-three (21%) patients showed CT evidence of proximal migration (median migration +6.0, IQR +4.5 to +7.9, range +4.1 to +10.0 mm). The median time to the 1st CT diagnosis of proximal migration was 11.8 (IQR 9.0 to 23.4, range, 1.0 to 88.7) months. Based on 329.9 years of follow-up data, it can be estimated that there will be one proximal migration per 10 person-years of follow-up. Full details on the frequencies, magnitudes and timings of proximal migration are illustrated in Figure 6.2 and Figure 6.3. Kaplan-Meier survival analysis for estimating freedom from proximal migration will be discussed later in this chapter.

Figure 6.2 Magnitudes and frequencies of proximal stent-graft migration

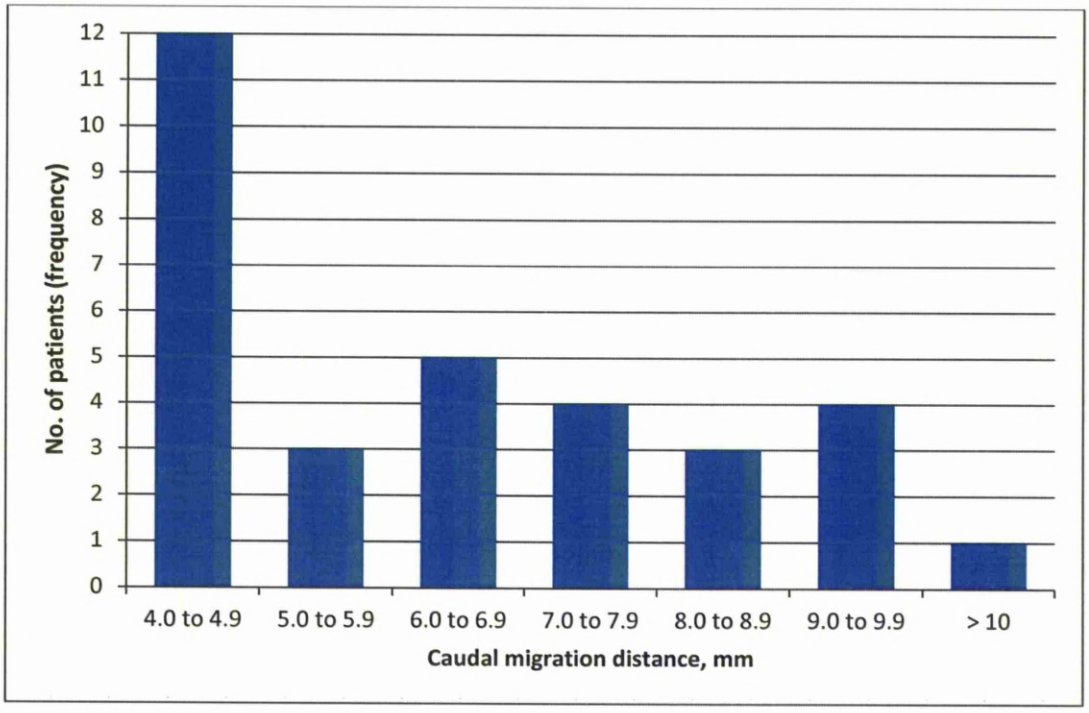
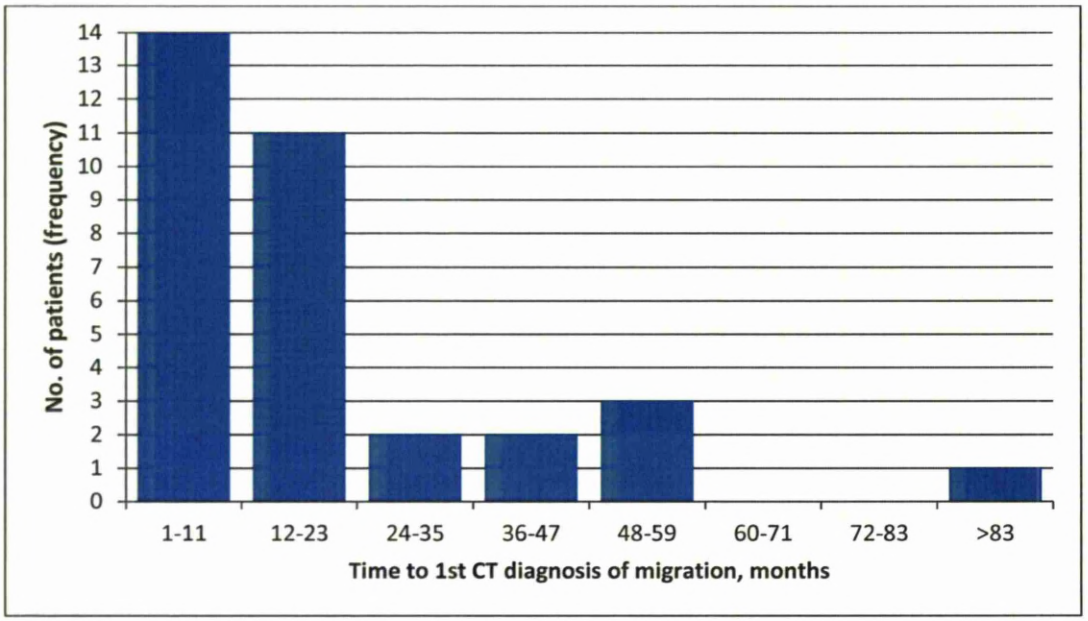


Figure 6.3 Time to 1st CT diagnosis of proximal migration



Distal (iliac) limb migration

Using data from 154 patients, a total of 259 iliac limbs were assessed for the presence of distal migration. In 36 patients (49 CIAs) a CLL was unable to be constructed or there was an absence of a deployed iliac limb (e.g. tube or AUI device) (Figure 6.1). Of the 259 limbs assessed 34 (13%) showed CT evidence of cranial migration, median -6.1 mm (IQR -7.8 to -5.1, range -21.3 to -4.1) mm. Based on 276 person-years of iliac limb follow-up, it is estimated that there will be one iliac limb migration per 9.9 years of follow-up. Details on the magnitude and timings for distal migration of both ipsilateral and contralateral limbs are illustrated in Figure 6.4 and Figure 6.5.

Figure 6.4 Magnitudes and frequencies of *distal* stent-graft migration

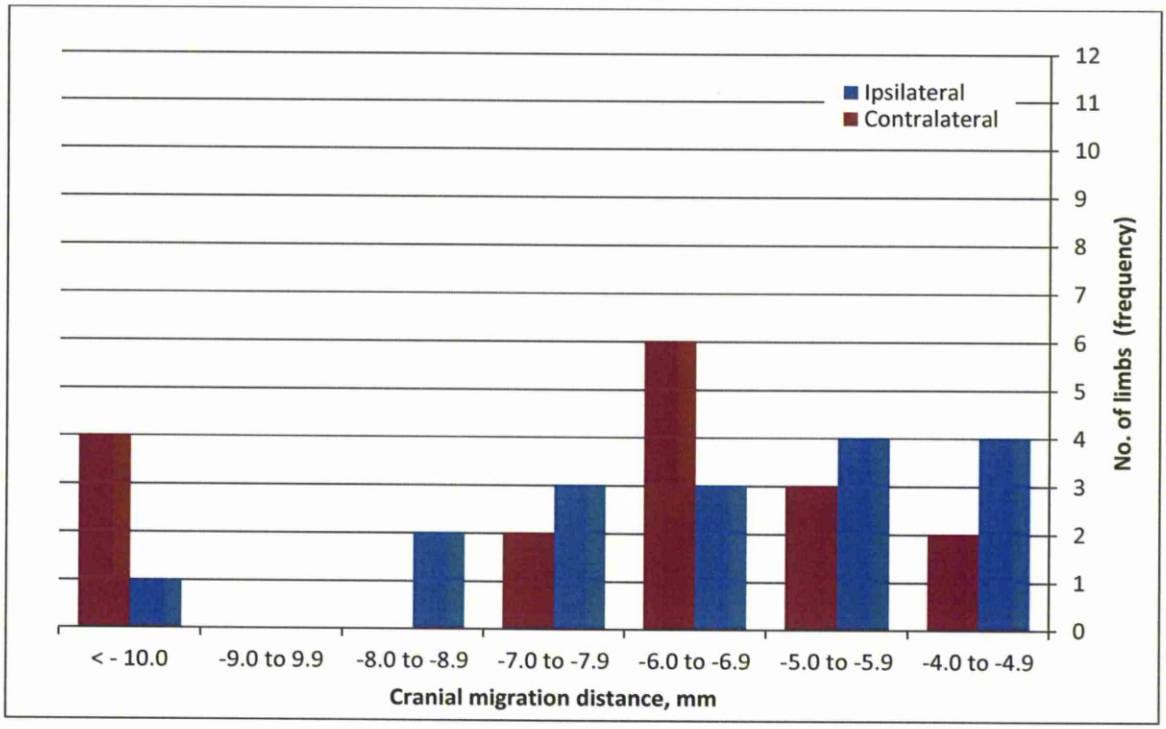
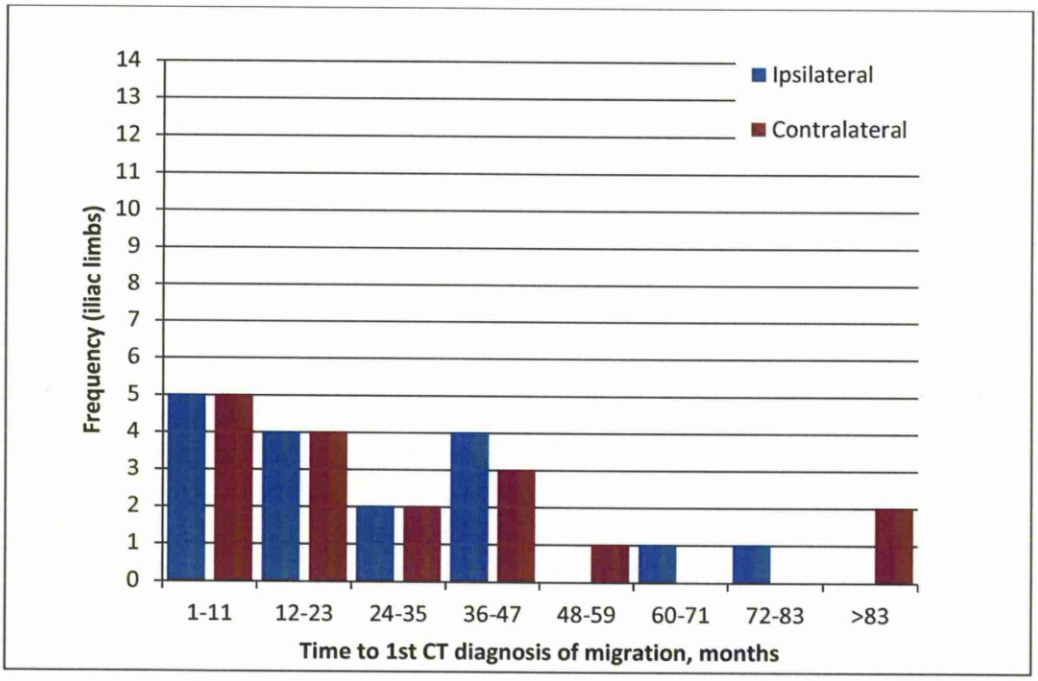


Figure 6.5 Time to 1st CT diagnosis of distal (iliac) limb migration (based on the assessment of 259 limbs)



Any (proximal or distal) migration

The number of patients experiencing either a proximal or distal (iliac) limb migration was 52 (34%) and the number of patients with proximal and at least one iliac limb migration was 28 (24%).

6.3.4 Timing of migration

Kaplan-Meier survival analysis, using interval censoring, estimated that the probability of being free from proximal migration at 12, 24 and 36 months were 82% (95% CI, 75%-89%), 77% (95% CI, 70%-85%) and 77% (95% CI, 70%-85%), respectively. Data using standard survival approaches, with event time (*T*) at the beginning, midpoint and the end of the interval are also provided for comparison (Table 6.4 and Figure 6.6).

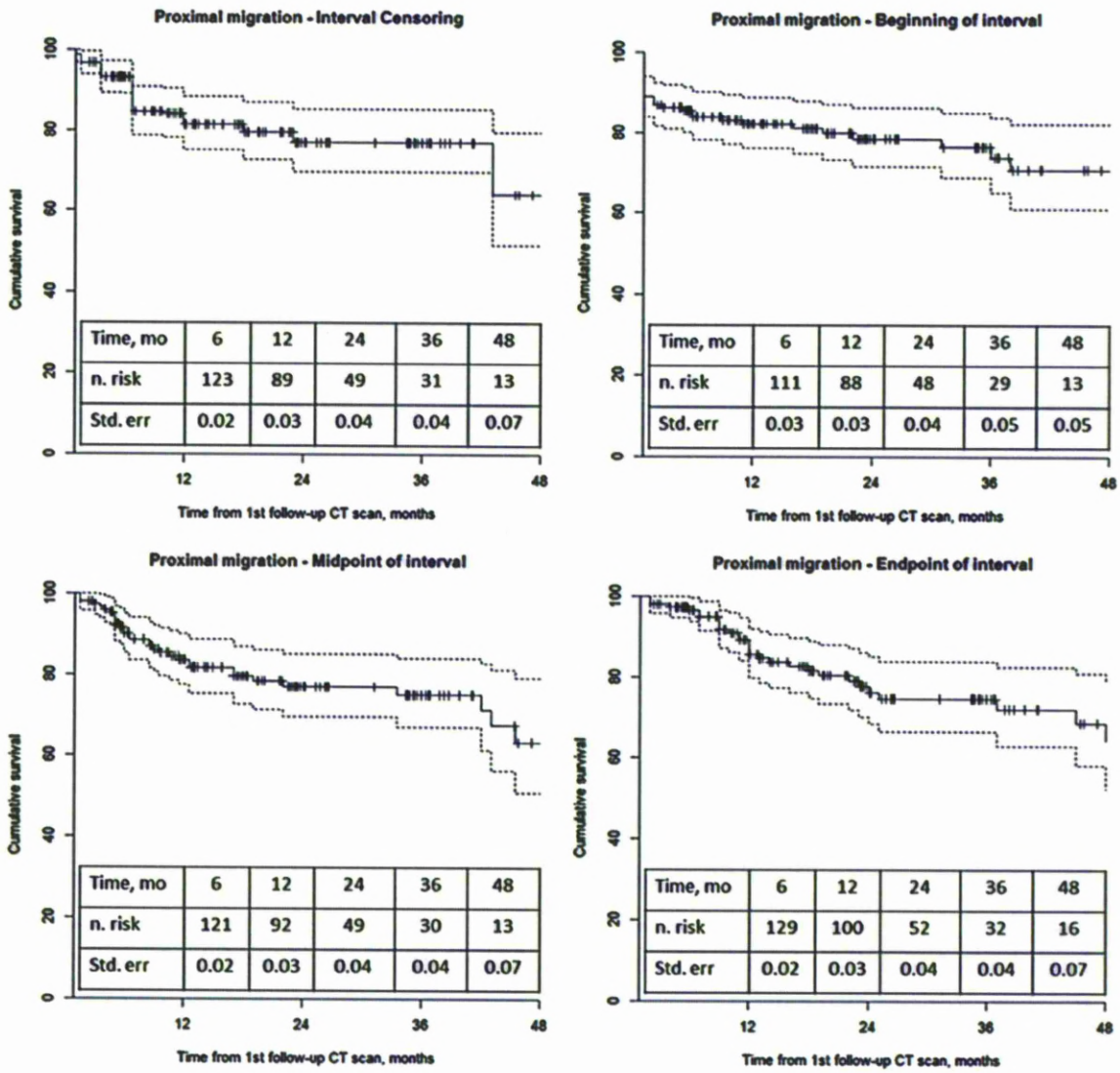
Table 6.4 Comparison of survival estimation approaches for proximal migration (multicentre data). Percentages relate to the proportion of patients free from migration.

	Interval censoring			Beginning of interval		
Time, mo	**n. risk**	**survival**	**95% CI**	**n. risk**	**survival**	**95% CI**
12	89	82%	75% to 89%	88	82%	76% to 89%
24	49	77%	70% to 85%	48	79%	72% to 86%
36	31	77%	70% to 85%	29	74%	65% to 84%
48	13	64%	51% to 80%	13	71%	61% to 82%

	Midpoint of interval			End of interval		
Time, mo	**n. risk**	**survival**	**95% CI**	**n. risk**	**survival**	**95% CI**
12	92	84%	78% to 90%	92	84%	78% to 90%
24	49	77%	70% to 85%	49	77%	70% to 85%
36	30	75%	67% to 84%	30	75%	67% to 84%
48	13	63%	51% to 79%	13	63%	51% to 79%

Mo, months. n, number of patients. CI, confidence interval.

Figure 6.6 Kaplan-Meier survival analysis illustrating freedom from proximal stent-graft migration using a combination of event time definitions (multicentre data).



95% confidence intervals (dotted lines); CT, computed tomography; std. err, standard error. Percentage values across the y-axis relate to the proportion of patients free from migration.

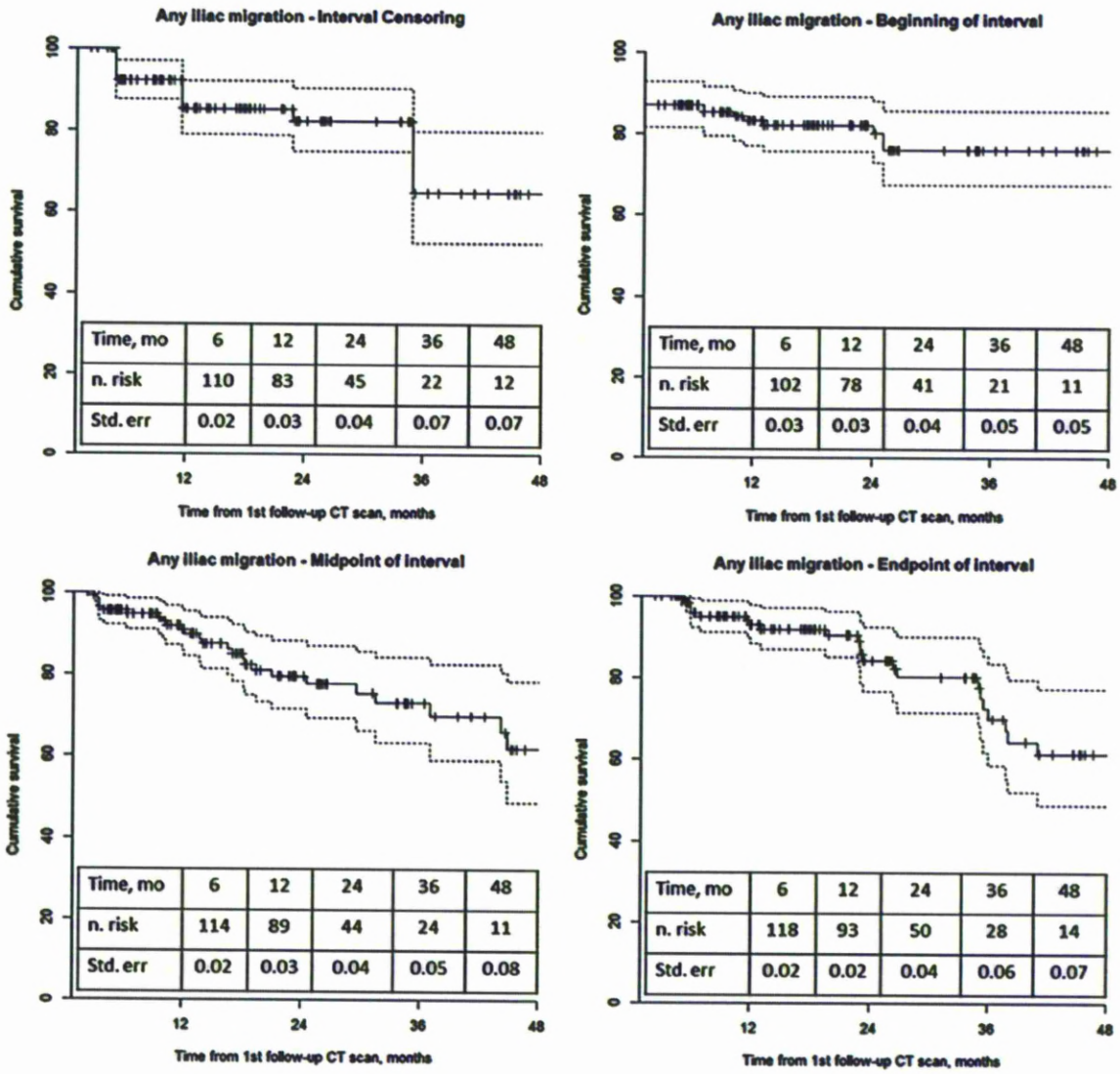
As previously stated, a total of 259 iliac limbs were assessed for the presence of distal stent-graft migration. Survival analyses were undertaken for ipsilateral and contralateral iliac limbs and for evidence of *any* iliac limb migration. Kaplan-Meier survival analysis, using interval censoring, estimated that the probability of being free from any iliac limb migration at 12, 24 and 36 months were 85% (95%CI 79% to 92%), 82% (95%CI 75% to 90%) and 65% (95%CI 52% to 80%), respectively (Table 6.5, Figure 6.7). For separate iliac limbs, the ipsilateral migration rate at 12, 24 and 36 months were 94% (95%CI 90%-98%), 87% (95%CI 80%-95%) and 76% (95%CI 64%-89%), respectively (Table 6.6, Figure 6.8). Contralaterally, freedom from migration rates were similar 92% (95%CI 93%-100%), 92% (95%CI 87%-98%) and 78% (95% CI 67%-90%), respectively (Table 6.6, Figure 6.9).

Table 6.5 A comparison of survival estimation approaches for freedom from any iliac limb migration. Percentages relate to the proportion of patients free from migration.

	Interval censoring			Beginning of interval		
Time, mo	**n. risk**	**survival**	**95% CI**	**n. risk**	**survival**	**95% CI**
12	83	85%	79% to 92%	78	83%	77% to 90%
24	45	82%	75% to 90%	41	80%	73% to 88%
36	22	65%	52% to 80%	21	76%	68% to 86%
48	12	65%	52% to 80%	11	76%	68% to 86%
	Midpoint of interval			**End of interval**		
Time, mo	**n. risk**	**survival**	**95% CI**	**n. risk**	**survival**	**95% CI**
12	89	91%	86% to 96%	93	93%	89% to 98%
24	44	80%	72% to 88%	50	84%	77% to 93%
36	24	73%	63% to 84%	28	70%	59% to 84%
48	11	62%	49% to 79%	13	62%	49% to 78%

Mo, months. n, number of patients. CI, confidence interval.

Figure 6.7 *Kaplan-Meier survival analysis illustrating freedom from any iliac limb migration using a combination of event time definitions (multicentre data).*



95% confidence intervals (dotted lines); CT, computed tomography; std. err, standard error. Percentage values across the y-axis relate to the proportion of patients free from migration.

Table 6.6 Comparison of survival estimation approaches for individual iliac limb migration (multicentre data). Percentages relate to the proportion of iliac limbs free from migration.

Ipsilateral	Interval censoring			Beginning of interval		
Time, mo	n. risk	survival	95% CI	n. risk	survival	95% CI
12	81	95%	90% to 99%	78	92%	87% to 97%
24	45	89%	82% to 96%	43	85%	77% to 94%
36	26	77%	67% to 90%	26	82%	74% to 92%
48	14	77%	67% to 90%	14	82%	74% to 92%

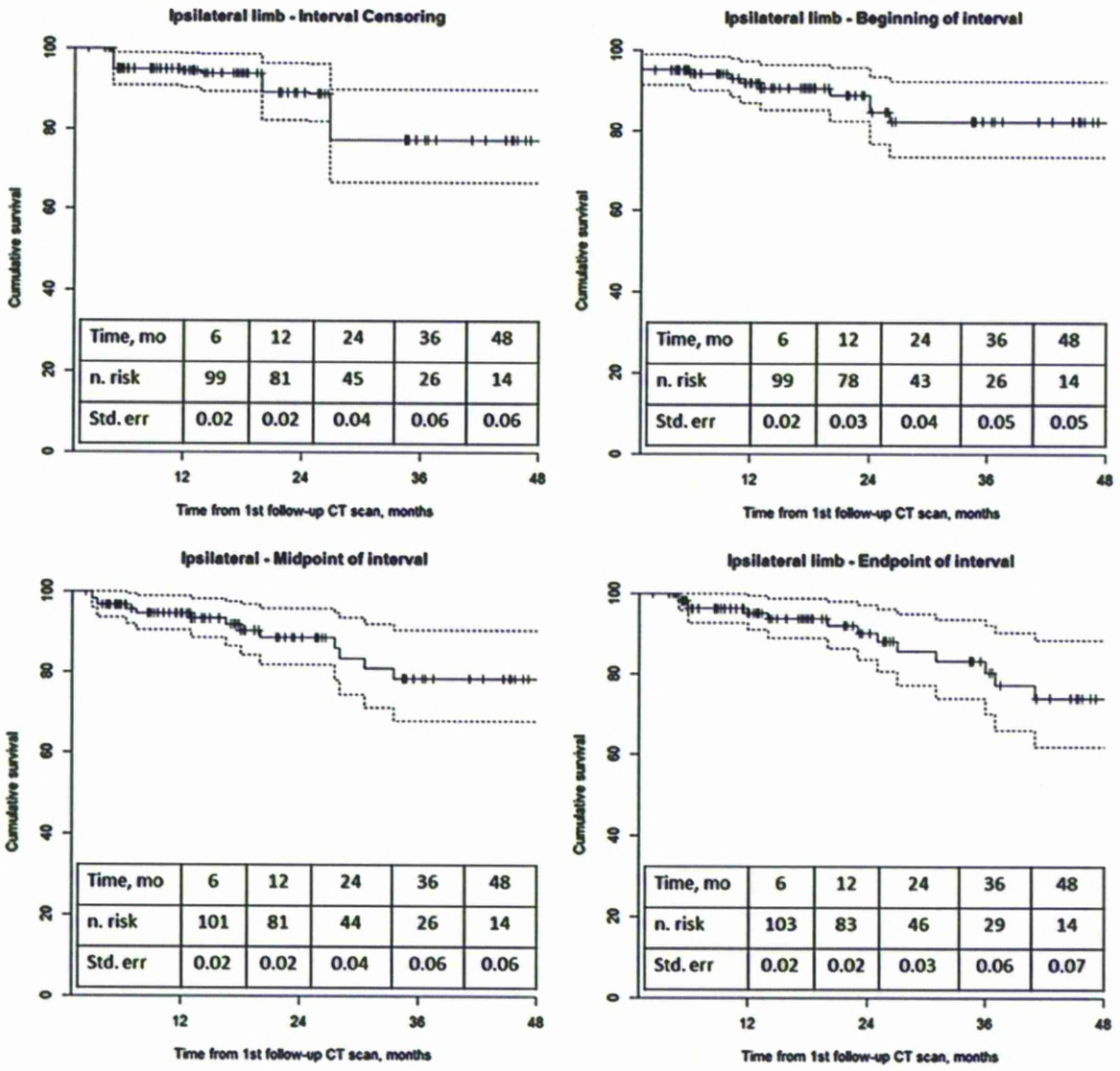
	Midpoint of interval			End of interval		
Time, mo	n. risk	Survival	95% CI	n. risk	survival	95% CI
12	81	95%	91% to 99%	82	95%	91% to 99%
24	44	98%	82% to 96%	46	90%	84% to 97%
36	26	79%	68% to 91%	29	80%	70% to 92%
48	14	79%	68% to 91%	14	74%	62% to 89%

Contralateral	Interval censoring			Beginning of interval		
Time, mo	n. risk	survival	95% CI	n. risk	survival	95% CI
12	86	95%	91% to 99%	83	92%	88% to 97%
24	49	90%	84% to 97%	47	88%	82% to 95%
36	24	76%	65% to 89%	24	82%	73% to 92%
48	15	76%	65% to 89%	15	82%	73% to 92%

	Midpoint of interval			End of interval		
Time, mo	n. risk	survival	95% CI	n. risk	Survival	95% CI
12	85	94%	90% to 98%	86	94%	90% to 99%
24	48	90%	84% to 96%	49	90%	84% to 97%
36	25	81%	71% to 92%	28	82%	72% to 93%
48	15	77%	67% to 90%	16	75%	63% to 90%

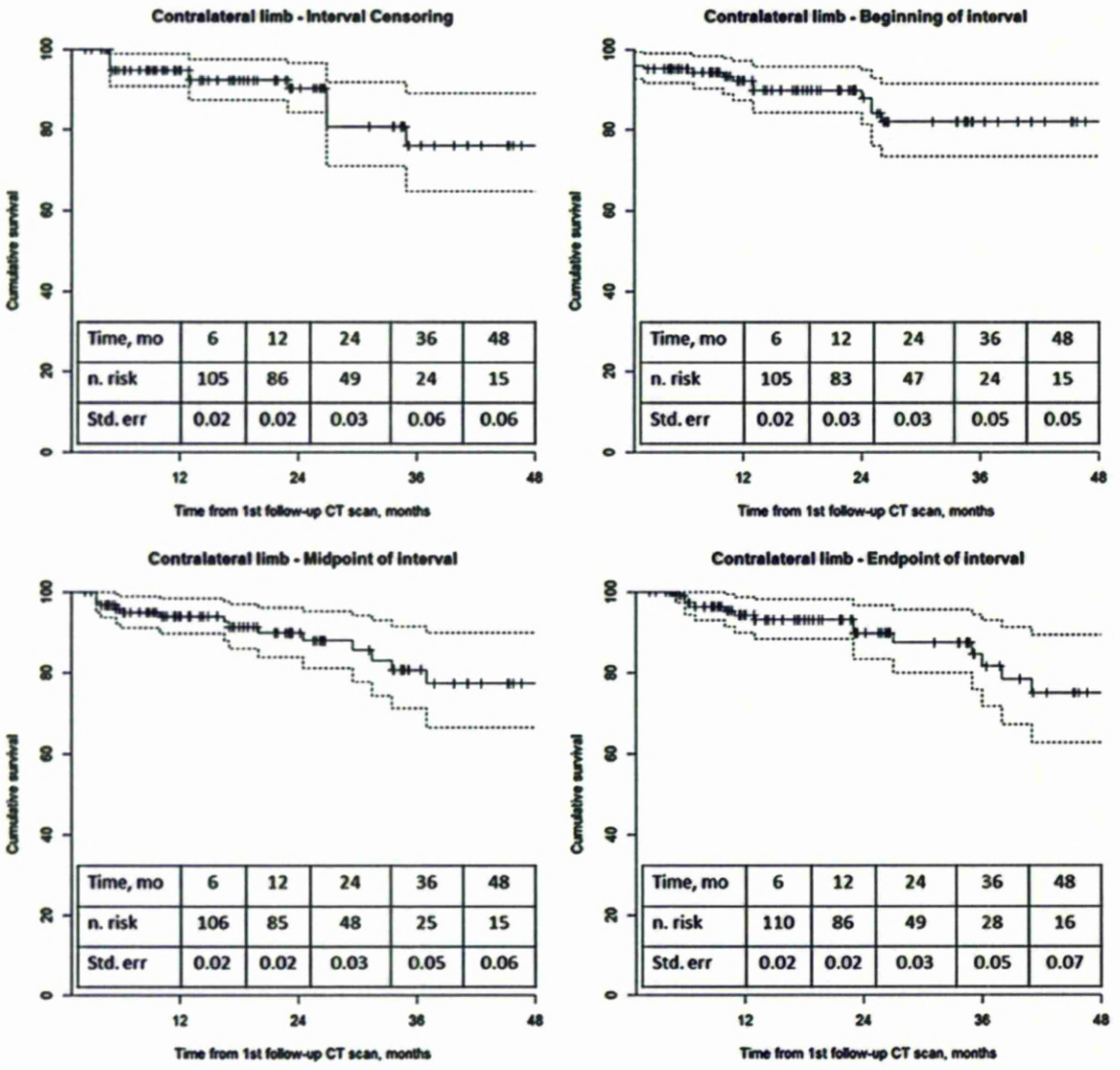
Mo, months. n, number of patients. CI, confidence interval.

Figure 6.8 *Kaplan-Meier survival analysis illustrating freedom from ipsilateral limb migration using a combination of event time definitions (multicentre data)*



95% confidence intervals (dotted lines); CT, computed tomography; std. err, standard error. Percentages relate to the proportion of iliac limbs free from migration.

Figure 6.9 Kaplan-Meier survival analysis illustrating freedom from contralateral limb migration using a combination of event time definitions (multicentre data)



95% confidence intervals (dotted lines); CT, computed tomography; std. err, standard error. Percentages relate to the proportion of iliac limbs free from migration.

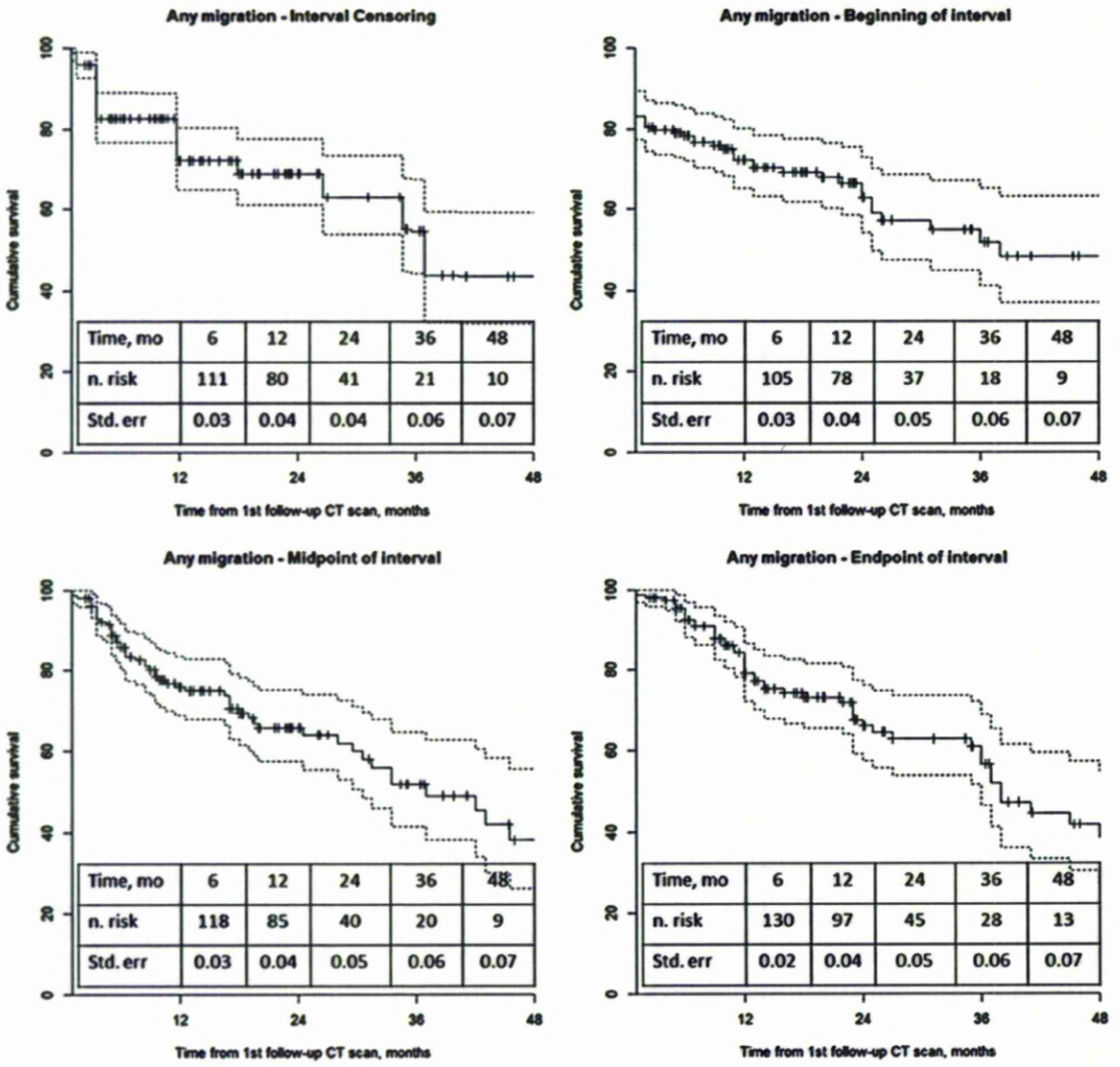
Freedom from any (proximal or distal iliac limb) migration at 12, 24 and 36 months were 72% (95%CI 65%-80%), 69% (95%CI 61%-78%) and 50% (95%CI 44%-67%), respectively (Figure 6.10 and Table 6.7).

Table 6.7 A comparison of survival estimation approaches for freedom from any migration (proximal or distal). Percentages relate to the proportion of patients free from migration.

	Interval censoring			Beginning of interval		
Time, mo	**n. risk**	**survival**	**95% CI**	**n. risk**	**survival**	**95% CI**
12	80	72%	65% to 80%	78	72%	65% to 80%
24	41	69%	61% to 78%	37	63%	54% to 73%
36	21	55%	44% to 67%	18	52%	41% to 65%
48	10	44%	32% to 59%	9	48%	37% to 63%
	Midpoint of interval			**End of interval**		
Time, mo	**n. risk**	**survival**	**95% CI**	**n. risk**	**survival**	**95% CI**
12	85	76%	69% to 84%	97	79%	72% to 87%
24	40	66%	58% to 75%	45	66%	58% to 76%
36	20	52%	42% to 65%	28	57%	47% to 69%
48	9	38%	26% to 56%	13	39%	27% to 55%

Mo, months. n, number of patients. CI, confidence interval.

Figure 6.10 Kaplan-Meier survival analysis illustrating freedom from any migration (proximal or iliac limb) using a combination of event time definitions (multicentre data)



95% confidence intervals (dotted lines); CT, computed tomography; std. err, standard error. Percentages relate to the proportion of patients free from migration.

Consideration must also be made for patients, where an iliac limb had been deployed but a CLL analysis was not possible (image quality reasons or occluded IIA). It could be theoretically possible that these limbs had undergone migration but because a CLL could not be generated, then they could not be accounted for in the analysis. To account for this, two exploratory (sensitivity) analyses were undertaken with the following assumptions. 1) any deployed iliac limb that could not be assessed would be considered to have migrated by the second CT scan (6-months). It was also assumed that the previous CT scan would have been performed at 1-month (interval). The results of this analysis are presented in Figure 6.11 and Table 6.8. A second set 2) of assumptions were that any iliac limbs not assessed using a CLL were assumed to have migrated with a similar incidence (13%) and timings as those in assessed patients. The results of the second exploratory analysis are presented in Table 6.9 and Figure 6.12.

Table 6.8 Comparison between Kaplan Meier survival analysis (original data) and a modified dataset assuming migration at six months for missing values (Assumptions 1)

		n.risk		survival (%)		lower 95%CI		upper 95%CI	
	time, mo	Original dataset	Modified dataset	Original dataset	Modified dataset	Original dataset	Modified dataset	Original dataset	Modified dataset
Ipsilateral limb	12	82	107	94	95	90	92	98	99
	24	44	47	87	91	80	85	95	96
	36	36	26	76	74	64	63	89	87
	48	15	15	76	74	64	63	89	87
Contralateral limb	12	84	84	92	76	87	69	98	83
	24	49	49	92	75	87	68	98	83
	36	24	24	78	64	67	54	90	75
	48	13	13	78	64	67	54	90	75

CI, confidence interval. Mo, months. All survival analyses were constructed using an interval censoring approach. For patients with missing iliac migration data the incidence of migration was assumed to be at 6-months with a prior CT scan at 1 month. Percentages relate to the proportion of iliac limbs free from migration.

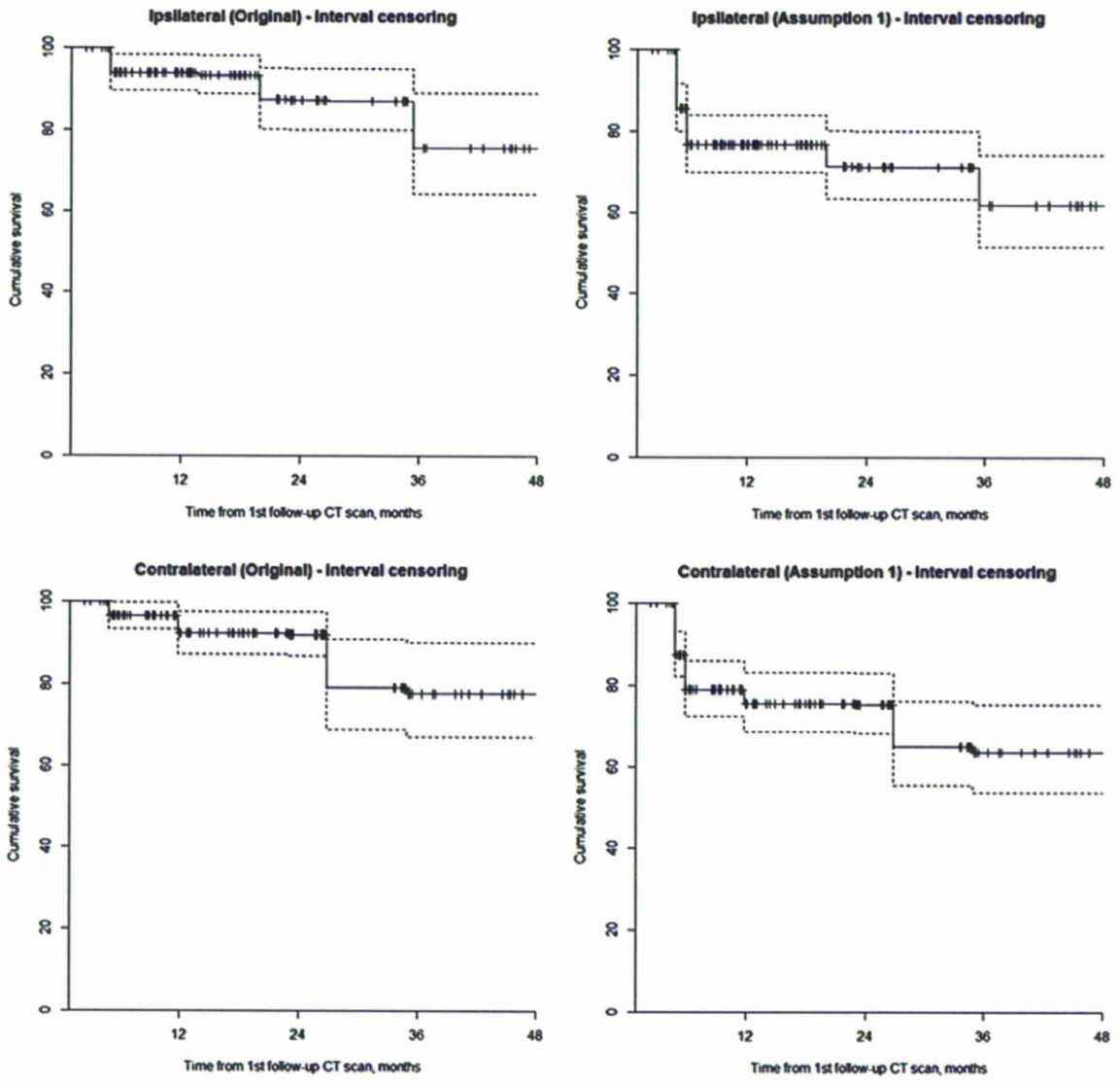
For assumption one, when comparing the original and modified datasets, there were no changes in the freedom from ipsilateral iliac limb migration rates during follow-up. For contralateral limbs, the migration rate increased by between 14% and 16% across all follow-up times, when switching from the original to the modified dataset. There was a narrowing of the 95% CI when using the modified dataset reflecting the increased sample size. For the second assumption, there were little differences in the survival rates when switching between datasets (1% to 4%). Again, there was a reduction in the size of the confidence intervals when using the larger (modified) datasets. Although the use of a modified dataset decreases, the confidence intervals for the survival estimates questions regarding the most appropriate scenario exist. With data missing on 31 iliac limbs it is likely that there will have been migration in some limbs and, therefore, when interpreting the survival estimates this point must be considered.

Table 6.9 Comparison between Kaplan Meier survival analysis (original data) and a dataset assuming migration a similar migration rate for missing values (Assumptions 2)

		n.risk		survival (%)		lower 95%CI		upper 95%CI	
	time, mo	Original dataset	Modified dataset	Original dataset	Modified dataset	Original dataset	Modified dataset	Original dataset	Modified dataset
Ipsilateral limb	12	82	107	94	95	90	92	98	99
	24	44	47	87	91	80	85	95	96
	36	36	26	76	74	64	63	89	87
	48	15	15	76	74	64	63	89	87
Contralateral limb	12	84	109	92	94	87	90	98	98
	24	49	52	92	94	87	89	98	98
	36	24	24	78	74	67	63	90	87
	48	13	13	78	74	67	63	90	87

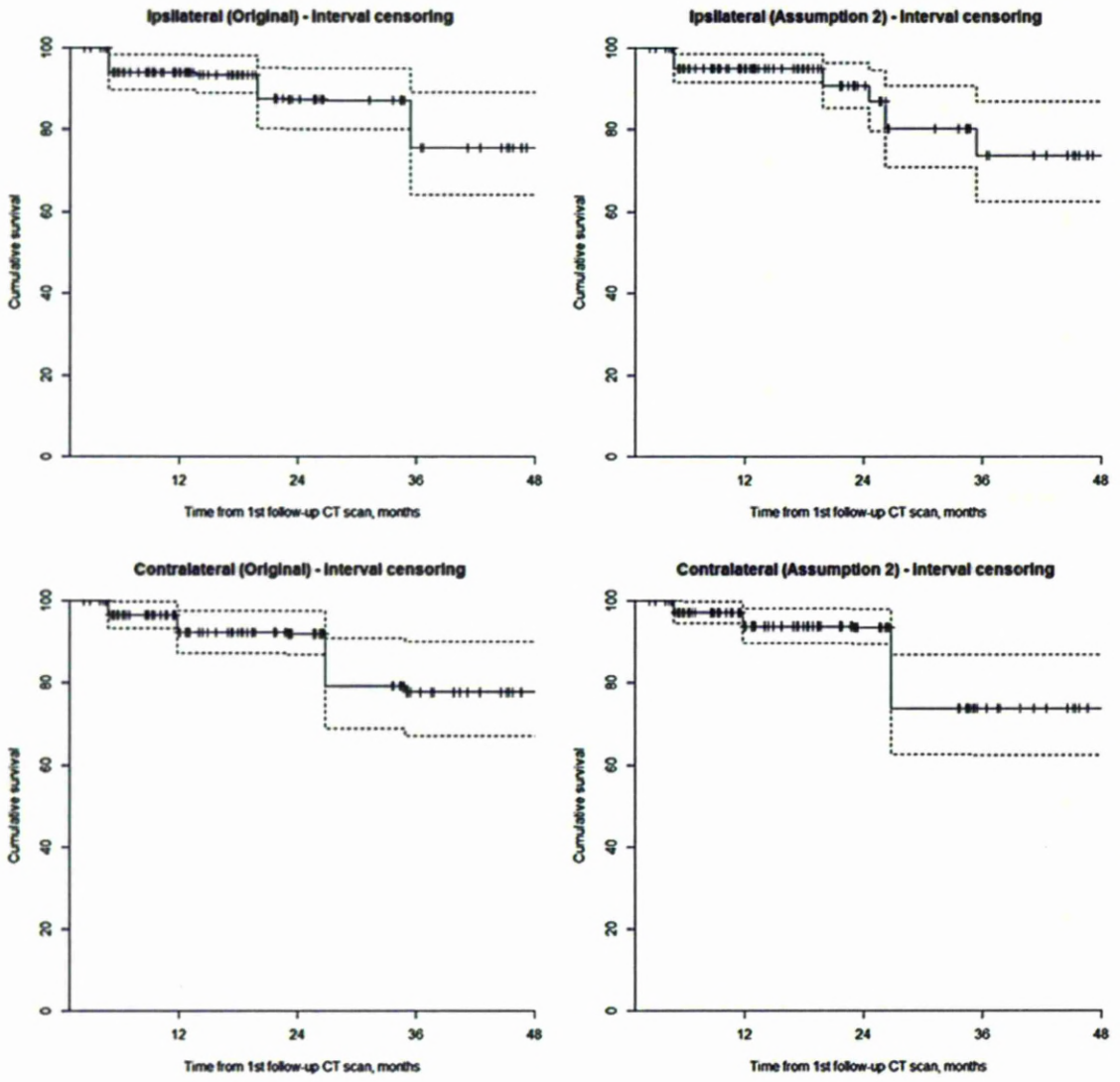
CI, confidence interval. Mo, months. All survival analyses were constructed using an interval censoring approach. For patients with missing iliac migration data the incidence of migration was assumed to mirror that of the original dataset. The missing cases were then modeled as either migrated or non-migrated with interval, event time or maximum follow-up reflect the mean data from the original dataset. Percentages relate to the proportion of iliac limbs free from migration.

Figure 6.11 Sensitivity analysis, Kaplan-Meier plot, using interval censoring, of freedom from ipsilateral and contralateral limb migration assuming a 6 month migration time for all non-assessed iliac limbs(Original data versus Assumption 1)



95% confidence intervals (dotted lines); CT, computed tomography; std. err, standard error. Percentages relate to the proportion of iliac limbs free from migration.

Figure 6.12 Kaplan Meier survival analysis, using interval censoring for a modified dataset assuming a similar migration rate to those assessed using a CLL



95% confidence intervals (dotted lines); CT, computed tomography; std. err, standard error. Percentages relate to the proportion of iliac limbs free from migration.

6.3.5 Migration-related complications and reintervention

Complications are an accepted part of FEVAR. Endoleak, thrombosis, graft kinking and component fracture can all result from stent-graft migration but can also be attributed to other causes. In view of the number of participating centres, migration and complication definitions and data collected within the GLOBALSTAR registry, it was not always possible to ascertain the direct cause a complication or subsequent reintervention. However, it is plausible that the incidence of these events would be greater in a cohort of patients demonstrating evidence of stent-graft migration.

Forty-five endoleaks were present in 37 (24%) patients during follow-up, they were, however, statistically no more or less prevalent in patients with proximal stent-graft migration (Fisher's Exact test, P=0.13) (Table 6.10). Graft-related endoleaks (types 1 and 3) were present in 16 patients (13%) but only three patients (9%) with a graft-related endoleak had CT evidence of proximal stent-graft migration (Fisher's Exact test, P=0.15). Target vessels were lost in 10 (8%) patients, three of which had CT evidence of proximal migration (Fisher's Exact test, P=0.35) (Table 6.10). The number of cases of kinking and component fractures were statistically indifferent between proximal migration and non-migration groups (Fisher's Exact test, P=0.12 and P=0.54, respectively). Full details of complications are described in Table 6.10.

The iliac-related secondary events that could be related to distal iliac limb migration are distal type 1 endoleak and iliac limb occlusion. The distal type 1 endoleak rate has been previously reported in only one (0.6%) patient (Table 6.10). Limb occlusions were reported in 6 (3.9%) patients, the majority (five) were experienced within the first 30-days post-

implantation and were not considered to be associated with either proximal or distal fenestrated stent-graft migration. The individual per-limb failure rate was six out of 259 limbs (2.3%).

Table 6.10 Complications and their potential relationship with proximal migration during follow-up.

	Early			Late		
	No proximal migration (n=121)	**Proximal migration (n=33)**	**P value**	**No proximal migration (n=121)**	**Proximal migration (n=33)**	**P value**
Target vessel loss*	1 (1%)	2 (6%)	0.12	6 (5%)	1 (3%)	0.54
Endoleak						
Type 1 proximal	9 (7%)	2 (6%)		1 (1%)	1 (3%)	
Type 1 distal	1 (1%)	0 (0%)		0 (0%)	0 (0%)	
Type 3	0 (0%	0 (0%	0.85	2 (2%)	0 (0%)	0.39
Type 2	7 (6%)	3 (9%)		17 (14%)	2 (6%)	
Kinking*				8 (7%)	5 (15%)	0.12
Component fracture*				6 (5%)	1 (3%)	0.54
Component separation*				12 (11%)	6 (19%)	0.16
Limb occlusion*	5 (4%)	0 (0%)	0.29	1 (1%)	0 (0%)	0.79

P values for categorical variables (indicated by an asterisk*) are expressed using Fisher's exact test. All other categorical variables are expressed using the Chi-squared test. Component separation was defined as movement between the proximal and distal bodies ≥ 4 mm.

The reintervention rate within this multicentre cohort is likely to reflect the incidence of complications. On the whole, there was a relatively low number of complications and this is reflected in a low number of reinterventions (n=13, 8%) (Table 6.11). When comparing crude reintervention rates between a proximal migration cohort they were not statistically different (P=0.50). Interventions for endoleak were undertaken in five patients (3%), four of these were in patients without evidence of proximal migration and one in a patient with proximal migration (P=0.71). It has not been reflected within this paragraph or the accompanying table (Table 6.11) the relationship between the timings of the reinterventions and the timings of any migration. It may have been possible, that in some patients the migration may have occurred at a time point after the reintervention and, therefore, it would not be considered to be connected. This factor must be considered when interpreting these results.

Table 6.11 Reinterventional procedures encountered in the multicentre cohort

	Migration		P
	No (n=121)	Yes (n=33)	Value
Reintervention	10 (8%)	3 (9%)	0.50
Endoleak			
Balloon dilatation	1	1	
Embolisation	2	0	
Unspecified	1	0	
TV compromise			
PTA	1	0	
Stenting	3	1	
Unspecified	2	1	
Total	10	3	

Numbers represent the number of patients, no patient had more than a single reinterventional procedure. PTA, percutaneous transluminal angioplasty. *P* values were expressed using Fisher's exact test.

Reintervention resulting from the compromise of a target vessel were required in eight patients (5%). Again, it was difficult from reviewing the available data to ascertain if any cases were the unequivocal result of proximal stent-graft migration. There were six procedures for target vessel compromise in patients without evidence of proximal migration versus two reinterventions in those patients with proximal migration (P=0.54). Interventions favoured an endovascular approach and this may reflect the nature of the complications,

available treatment options and the physical status of the patients. It must be highlighted that other complications were reported (e.g. infection) but were not reported in the statistical analysis as they were thought to not be relevant to an investigation of device migration. Target vessel compromise was attributed to both occluded and threated (stenosed) vessels. For a vessel to be eligible for inclusion in this category, it needed to have been assigned a scallop or fenestration on the deployed endograft. By way of a further example, if the deployed device had a single renal scallop and the coeliac axis occluded at 24 months following repair, this could not have been categorised as a target vessel loss.

Survival estimates were generated for patients who experienced complications or required a secondary interventional procedure using the subgroup of patients with and without proximal migration (Figure 6.13). The Kaplan-Meier survival curves were constructed using interval censored data and the resultant survival functions were statistically compared using a log-rank test (Zhao and Sun, 2004, Kalbfleisch and Previce, 2002). Within this chapter the log-rank test was used to test the null hypothesis that there is no difference in probability of an event (complication or reintervention) at any time point for a group with proximal migration and a group without. The advantage of this technique is that the analysis is based on the times of the event and not just whether the event occurred. A limitation is that the log-rank test is purely a test of significance and it cannot provide an estimate of the size difference between the groups or a confidence interval (Bland and Altman, 2004). In order to understand the size of any effect difference a Cox proportional hazards model must be used, this will be focus of the next chapter. Based on the log-rank calculations from the survival curves in Figure 6.13, there were no statistical differences in the proximal survival functions for complications (P=0.84) and reinterventions (P=0.81).

Figure 6.13 Kaplan-Meier curves (using interval censoring) showing freedom from proximal migration in patients with and without a complication. Log-rank test, P=0.84

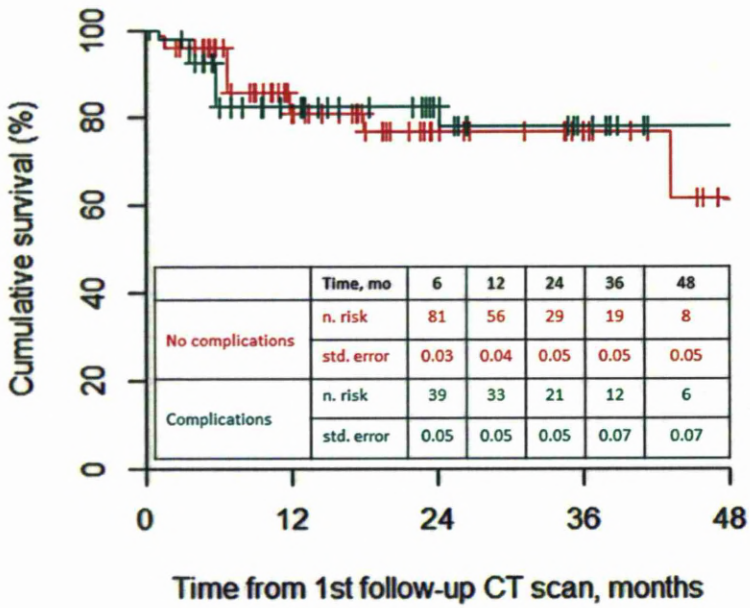
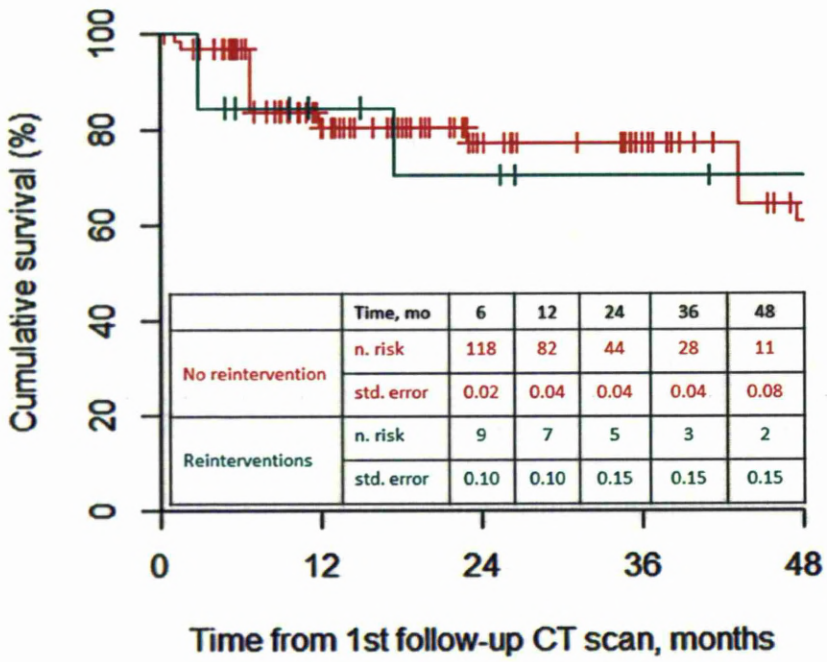


Figure 6.14 *Kaplan-Meier curves (using interval censoring) showing freedom from proximal migration in patients with and without reintervention. Log-rank test, P=0.81*



6.3.6 Migration rate by institution

The primary aim of this research was not to compare migration rates, either proximal or distal, between participating centres. However, data from Hospital A has previously been presented (Chapter 5) and has been incorporated into the multicentre analysis in this chapter (n=154). The data included in the chapter from Hospital A now contains an additional five patients and overall follow-up duration is longer. It is, however, important to see the differences in migration rates between Hospital A (pilot sample) and Hospitals B – I (additional multicentre data). Differences in migration data between the pilot and multicentre cohorts will now be presented and followed by an exploratory analysis of migration outcomes for individual centres.

Of the 154 patients included in the multicentre analysis 94 (61%) were recruited from Hospitals B - I. A comparison of baseline demographics, comorbidities and ASA physical status grading are described in Table 6.12. On the whole there were no statistically significant differences (P>0.05) in baseline demographics, comorbidities and ASA grades between patients from Hospital A and those from Hospitals B-I. The graft shape and target vessel configurations were also compared between Hospital A and Hospitals B - I (Table 6.13 & Table 6.14). Median (IQR) follow-up duration were 30.7 (14.3 to 49.6) months and 17.2 (8.4 to 26.1) months for Hospital A and Hospitals B – I, respectively. When assessed using a Mann-Whitney U test differences in follow-up duration were statistically significant (P<0.001). This difference could have been expected in that Hospital A was the first centre in the UK to embark on FEVAR procedures and was responsible for cascading training and developing a FEVAR service in hospitals B – I.

Table 6.12. Differences in demographics and comorbidities between patients from Hospital A and Hospitals B-I.

	Hospital A	Hospitals B - I	P value
Age, years	74 (SD 7)	74 (SD 7)	0.56
Maximum AAA diameter, mm	66 (IQR 60 - 73)	65 (IQR 59 - 70)	0.49
Gender, male	53 (88%)	88 (94%)	0.20
Ischaemic heart disease	31 (56%)	33 (46%)	0.16
Heart failure	3 (6%)	6 (8%)	0.41
Hypertension	33 (60%)	51 (71%)	0.14
Chronic renal insufficiency	6 (11%)	4 (6%)	0.21
Diabetes mellitus	4 (7%)	11 (15%)	0.13
ASA physical status grade			
I	1 (2%)	0 (0%)	0.16
II	16 (29%)	16 (26%)	[0.12]
III	37 (67%)	39 (63%)	
IV	1 (2%)	7 (11%)	

SD, standard deviation; IQR, inter-quartile range; ASA, American Society for Anesthesiology. For continuous data P values were calculated using either a t-test or Mann-Whitney U test. For categorical data either Fisher's Exact or Chi-squared test were used. Figures in the parentheses of categorical variables indicate the relative proportion for each cohort. Figures in the square brackets indicate the linear-by-linear association test.

Table 6.13. Differences in stent-graft configurations implanted in patients from Hospital A and Hospitals B-I.

	Hospital A	Hospitals B - I	P value
Bifurcated	60 (100%)	83 (88%)	0.02
AUI	0 (0%)	5 (5%)	[0.01]
Tube	0 (0%)	6 (6%)	

Numbers within the parentheses indicate the relative proportions for each cohort. P values were generated using the Chi-squared test [linear-by-linear association].

Table 6.14. Target vessel configuration used, comparison between patients from Hospital A and Hospitals B-I.

	Hospital A	Hospitals B - I	P value
CA			
Scallop	13 (22%)	16 (17%)	0.75
Fenestration	2 (3%)	4 (4%)	
SMA			
Scallop	34 (57%)	59 (63%)	0.59
Fenestration	18 (30%)	27 (29%)	
RT renal			
Scallop	3 (5%)	4 (4%)	0.74
Fenestration	52 (87%)	85 (90%)	
LT renal			
Scallop	4 (7%)	2 (2%)	0.03
Fenestration	53 (88%)	92 (98%)	[0.008]

No statistically significant differences were identified between the number of target vessels stented between Hospital A and Hospitals B-I (P>0.05). CA, coeliac axis. SMA, superior. mesenteric artery. RT, right. LT, left. Numbers within the parentheses indicate the relative proportions for each cohort. P values were generated using the Chi-squared test [linear-by-linear association].

Proximal migration

Proximal migration rates have been previously described for the pilot data and the full multicentre cohort. Proximal migration data will now be presented stratified for cohort (Hospital A versus Hospitals B – I). For Hospital A there were ten (17%) cases of proximal migration whereas for Hospitals B – I there were 23 (24%) cases according to thesis definitions. Median (IQR) proximal migration distances were +6.9 (+4.9 to +9.1) mm and +5.1 (+4.3 to +7.7) mm for Hospital A and Hospitals B – I, respectively. When assessed using a Mann-Whitney U there were no statistically significant differences between the two groups (P=0.167). Full details on the frequencies, magnitudes and times of proximal migration are illustrated in Figure 6.15 & Figure 6.16.

Figure 6.15. Magnitudes and frequencies of proximal stent-graft migration (comparison between Hospital A and Hospitals B – I)

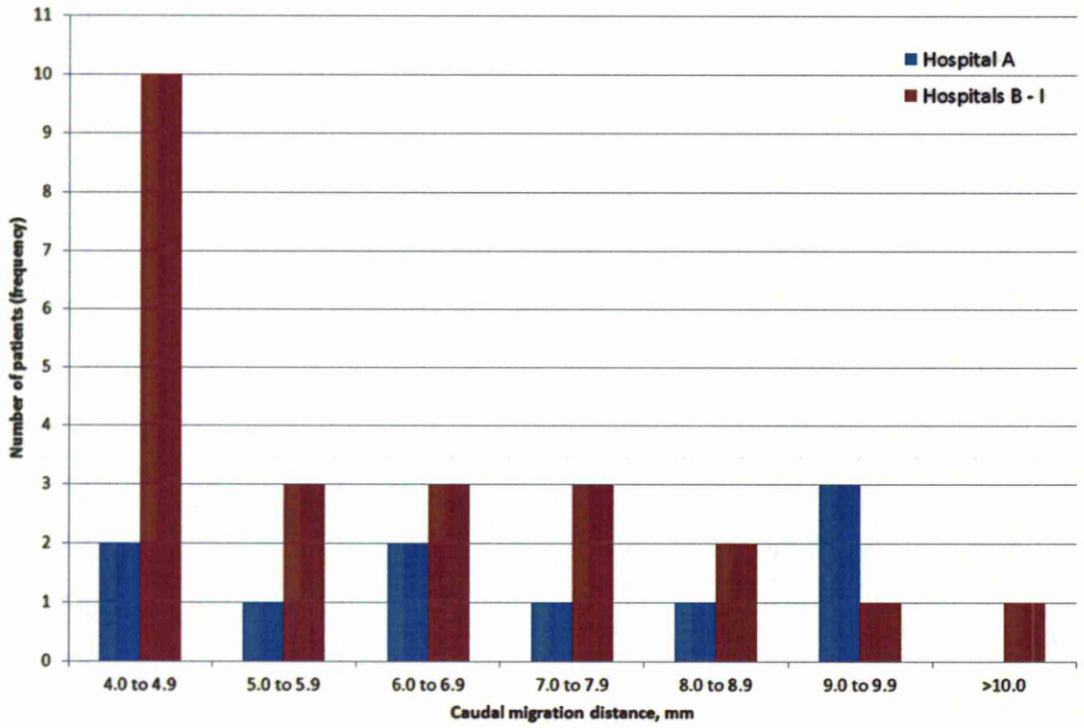
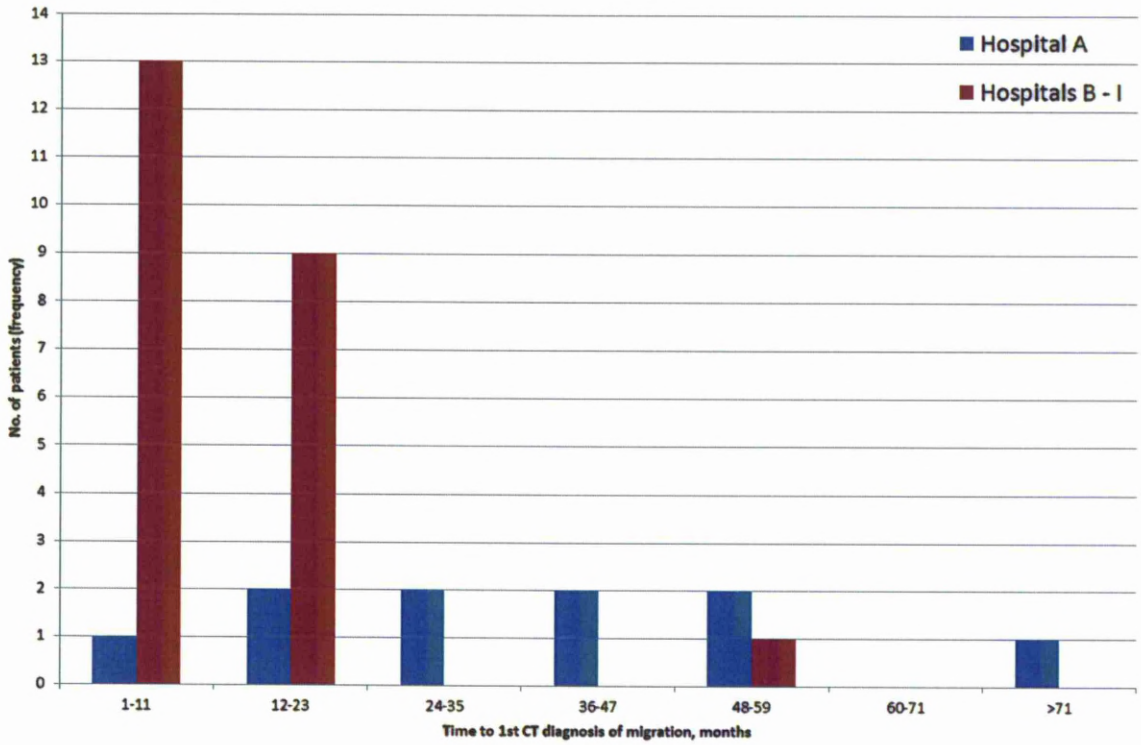
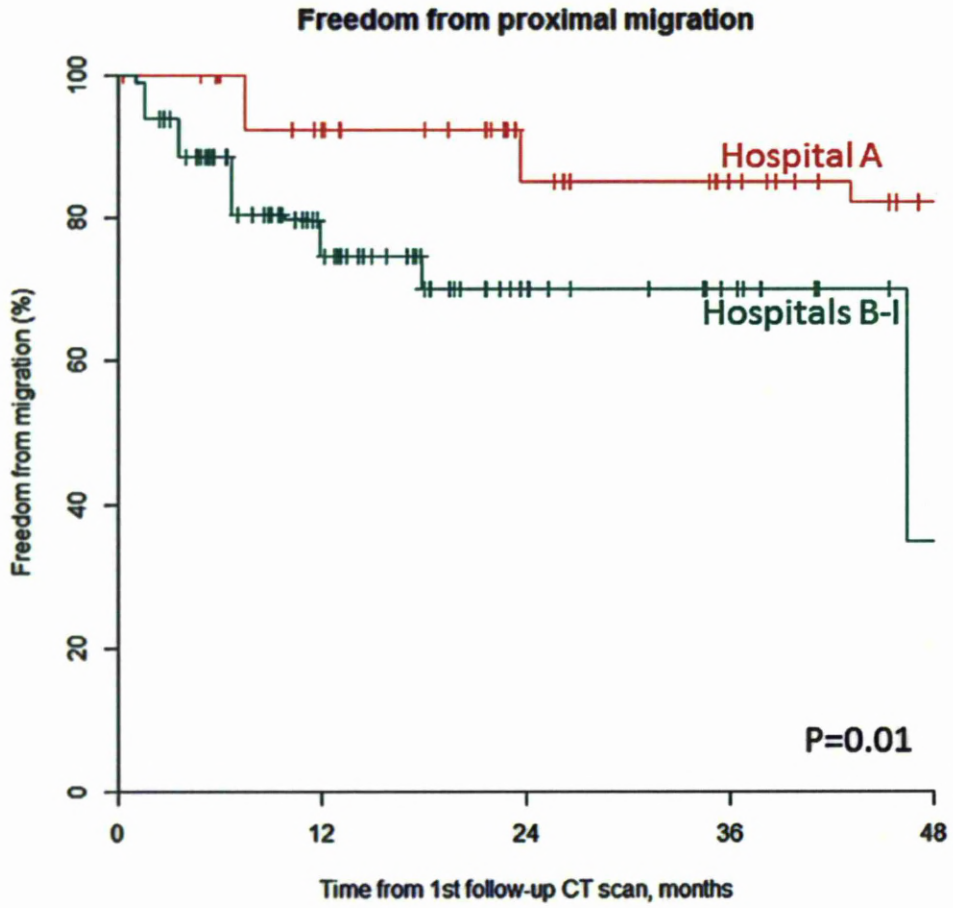


Figure 6.16 Time to 1st CT diagnosis of proximal migration (comparison between Hospital A and Hospitals B – I)



Kaplan-Meier survival analysis, using interval censoring, estimated that the probability of being free from proximal migration, at Hospital A, at 12, 24 and 36 months were 92% (95% CI, 86%-100%), 85% (95% CI, 75%-96%) and 85% (95% CI, 75%-96%), respectively. For Hospitals B – I the probability of being free from proximal migration at 12, 24 and 36 months were lower, 75% (95% CI, 65%-85%), 70% (95% CI, 59%-82%) and 70% (95% CI, 59%-82%), respectively. Comparison of the two survival curves (Figure 6.17) visually and using the log rank test (P=0.01) confirmed that the proximal migration hazards were statistically different between cohorts.

Figure 6.17. Kaplan-Meier survival analysis illustrating freedom from proximal stent-graft migration using interval-censoring (comparison between Hospital A and Hospitals B – I).



Time, months		6	12	24	36	48
Hospital A	Survival	100%	92.4%	85.1%	85.1%	82.2%
	n. risk	54	47	31	22	14
	std. err	0.0	0.04	0.05	0.05	0.06
Hospital B-I	Survival	88.6%	74.6%	69.8%	69.8%	34.9%
	n. risk	68	43	17	8	1
	std. err	0.03	0.05	0.06	0.06	0.25

Distal (iliac) limb migration

Using data from the two cohorts, a total of 110 iliac limbs were assessed for the presence of distal migration from Hospital A and 151 from Hospitals B - I. Of the 110 limbs assessed from Hospital A, 22 (20%) showed CT evidence of cranial migration. Median (IQR) migration was -7.0 (-8.0 to -4.5) mm and -6.1 (-7.4 to -5.2) mm for ipsi- and contralateral limbs, respectively. Of the 151 limbs assessed from Hospitals B – I 13 (9%) showed evidence of cranial migration. Median (IQR) migration was -5.8 (-6.6 to -5.1) mm and -9.6 (-15.0 to -5.1) mm for ipsi and contralateral limbs, respectively. Details on the magnitude and timings for distal migration of both ipsilateral and contralateral limbs are illustrated in Figure 6.4 and Figure 6.5.

Figure 6.18. *Magnitudes and frequencies of ipsilateral limb migration (comparison between Hospital A and Hospitals B – I)*

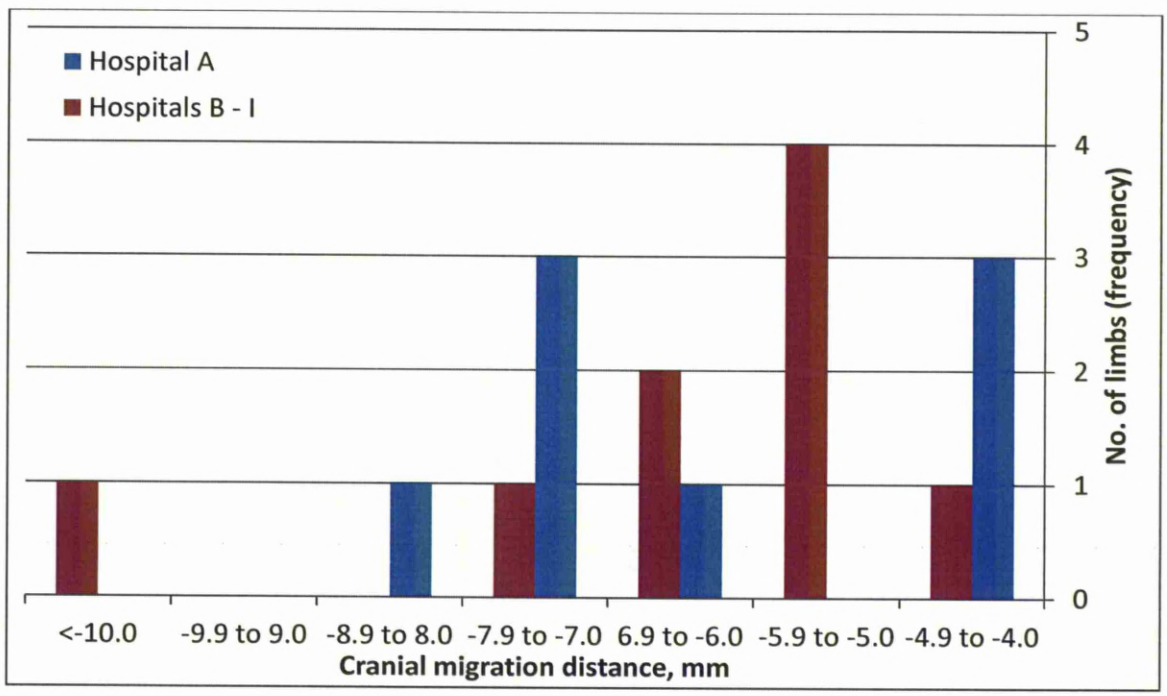


Figure 6.19. *Time to 1st CT diagnosis of ipsilateral limb migration (comparison between Hospital A and Hospitals B – I)*

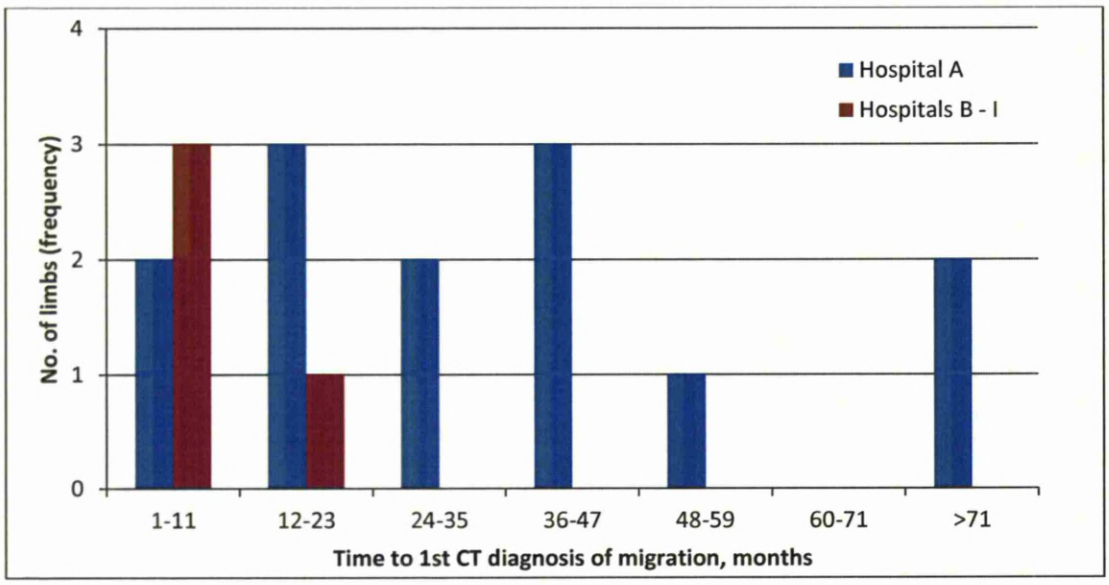


Figure 6.20. *Magnitudes and frequencies of contralateral limb migration (comparison between Hospital A and Hospitals B – I)*

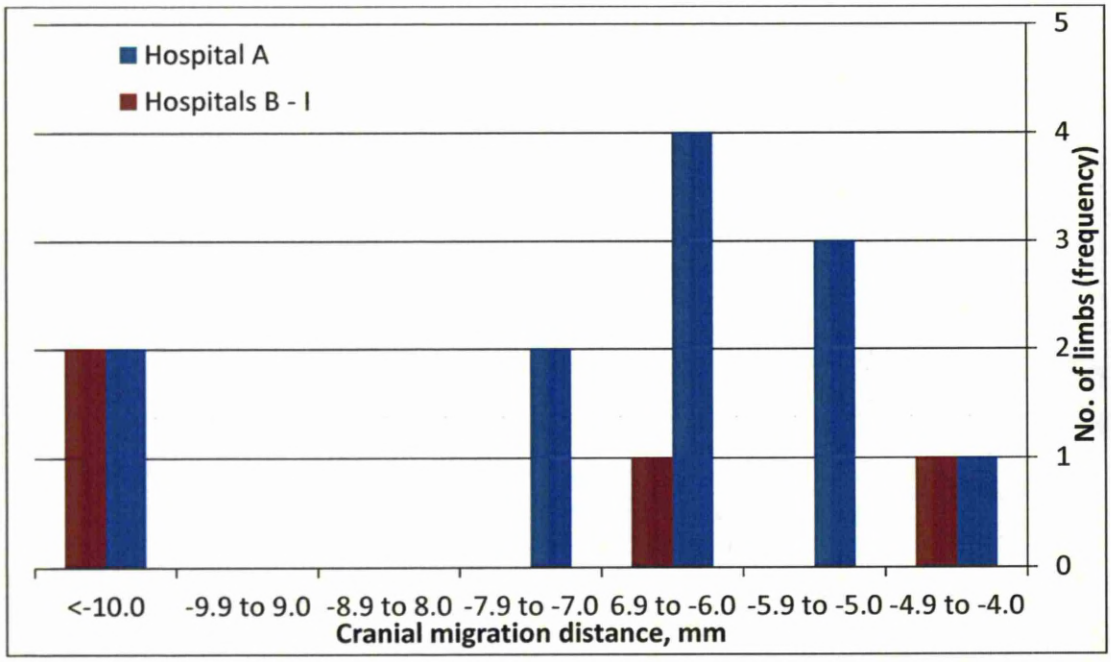
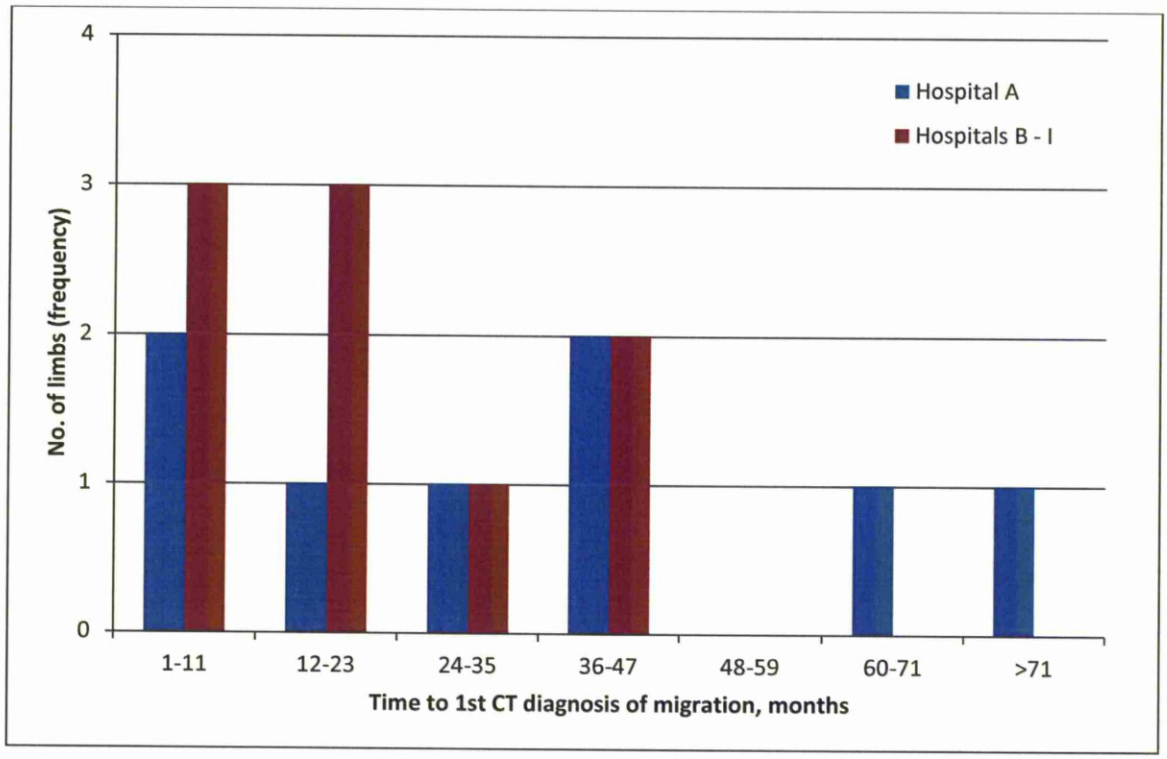
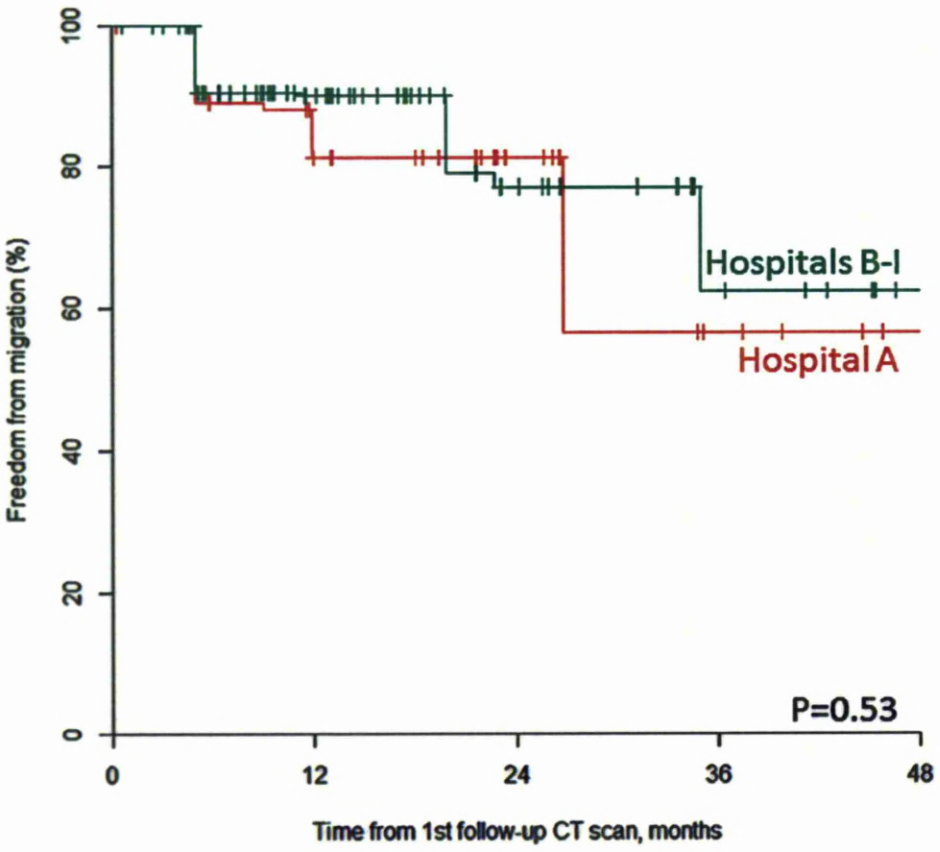


Figure 6.21 Time to 1st CT diagnosis of contralateral limb migration (comparison between Hospital A and Hospitals B – I)



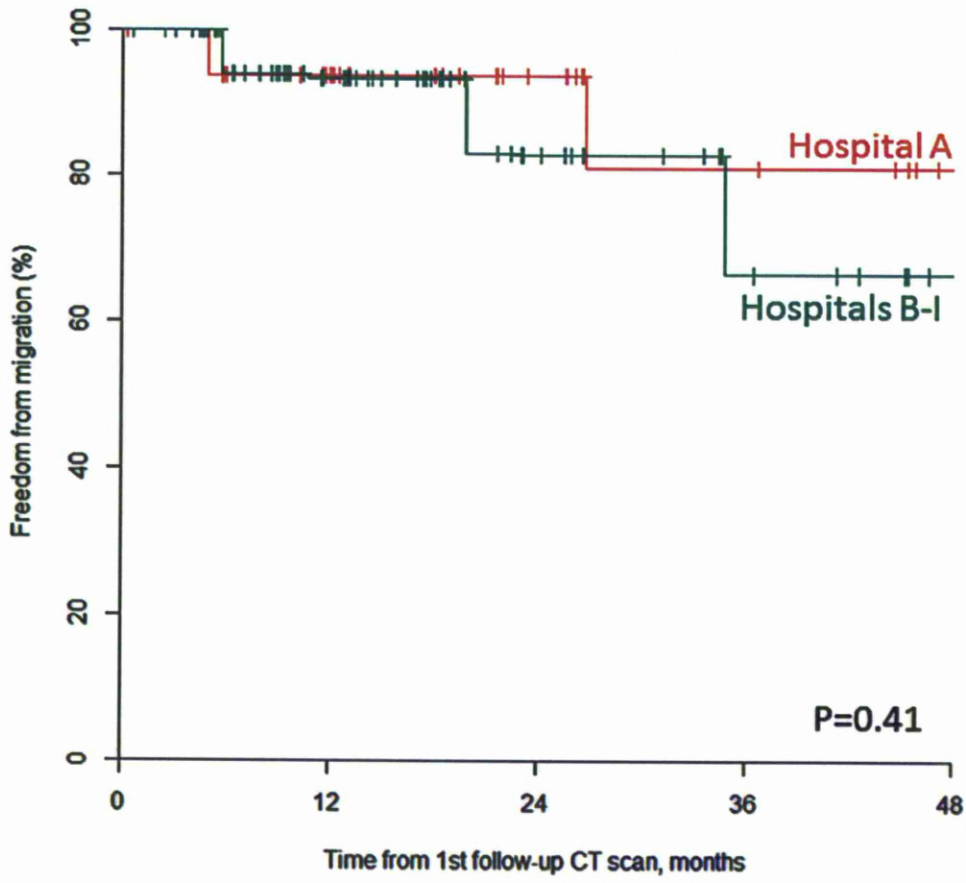
Kaplan-Meier survival analysis, using interval censoring, estimated that the probability of being free from any iliac limb migration, at Hospital A, at 12, 24 and 36 months were 89% (95% CI, 81%-98%), 81% (95% CI, 71%-92%) and 57% (95% CI, 42%-76%), respectively. For Hospitals B – I the probability of being free from proximal migration at 12, 24 and 36 months were similar at 90% (95% CI, 84%-97%), 77% (95% CI, 65%-92%) and 62% (95% CI, 44%-88%), respectively. Visual inspection of the two survival curves (Figure 6.22) and analysis of the log rank test (P=0.53) suggested, based on the available evidence, that the any iliac limb migration hazards were indifferent between cohorts. Data breakdowns by iliac limb type are present in Figure 6.23 & Figure 6.24.

Figure 6.22 Kaplan-Meier survival analysis illustrating freedom from any iliac limb migration using interval-censoring (comparison between Hospital A and Hospitals B – I).



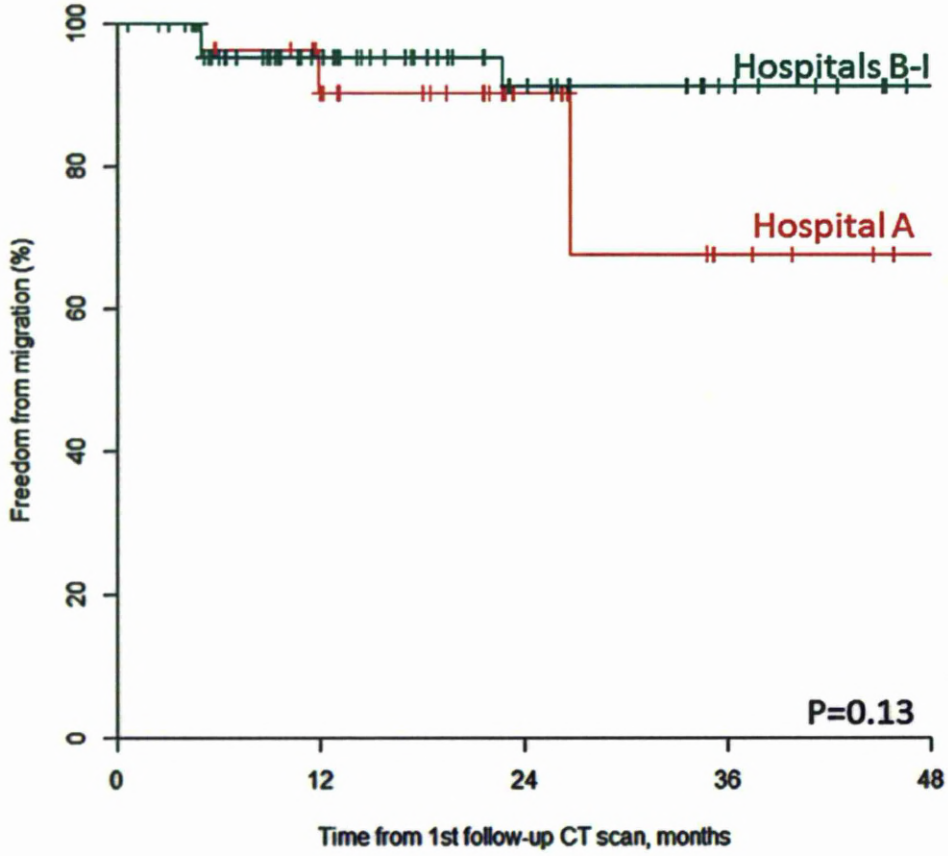
Time, months		6	12	24	36	48
Hospital A	Survival	89%	81%	81%	57%	57%
	n. risk	47	41	27	14	10
	std. err	0.04	0.05	0.05	0.09	0.09
Hospital B-I	Survival	90.5%	90.1%	77.1%	62.4%	62.4%
	n. Risk	62	45	20	8	2
	std. err	0.03	0.04	0.07	0.11	0.11

Figure 6.23. Kaplan-Meier survival analysis illustrating freedom from any ipsilateral iliac limb migration using interval-censoring (comparison between Hospital A and Hospitals B – I).



Time, months		6	12	24	36	48
Hospital A	Survival	94%	94%	94%	81%	81%
	n. risk	43	39	26	18	13
	std. err	0.03	0.03	0.03	0.07	0.07
Hospital B-I	Survival	94%	93%	83%	66%	66%
	n. risk	59	43	19	8	2
	std. err	0.03	0.03	0.06	0.12	0.12

Figure 6.24. *Kaplan-Meier survival analysis illustrating freedom from any contralateral iliac limb migration using interval-censoring (comparison between Hospital A and Hospitals B – I).*

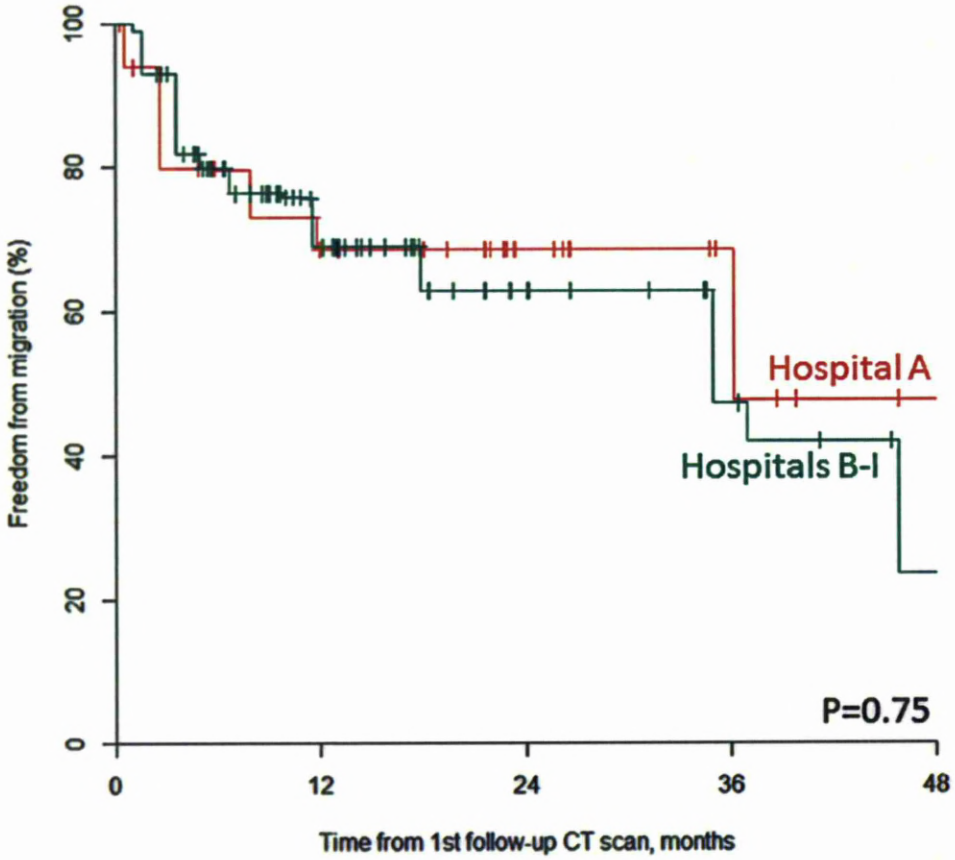


Time, months		6	12	24	36	48
Hospital A	Survival	96.4%	90.3%	90.3%	67.8%	67.8%
	n. risk	51	45	29	15	11
	std. err	0.03	0.04	0.04	0.09	0.09
Hospital B-I	Survival	95.3%	95.3%	91.3%	91.3%	91.3%
	n. risk	57	42	21	9	2
	std. err	0.03	0.03	0.05	0.05	0.05

Any migration

The number of patients experiencing either a proximal or distal (iliac) limb migration was 26 (43%) for Hospital A and 31 (33%) for Hospitals B – I (P=0.232). The number of patients with proximal migration and at least one iliac limb migration was two (3%) in Hospital A and five (5%) Hospital B- I (P=0.705). Kaplan-Meier survival analysis, using interval censoring, estimated that the probability of being free from any device migration, at Hospital A, at 12, 24 and 36 months were 69% (95% CI, 57%-82%), 69% (95% CI, 57%-82%) and 69% (95% CI, 57%-82%), respectively. For Hospitals B – I the probability of being free from any migration at 12, 24 and 36 months were 69% (95% CI, 59%-80%), 63% (95% CI, 52%-77%) and 47% (95% CI, 29%-76%), respectively. Visual inspection of the two survival curves (Figure 6.25) and analysis of the log rank test (P=0.75) suggested, based on the available evidence, that the any migration rates were indifferent between cohorts.

Figure 6.25. *Kaplan-Meier survival analysis illustrating freedom from any device migration using interval-censoring (comparison between Hospital A and Hospitals B – I).*



Time, months		6	12	24	36	48
Hospital A	Survival	79.7%	68.5%	68.5%	68.5%	47.7%
	n. risk	41	34	22	16	8
	std. err	0.05	0.06	0.06	0.06	0.09
Hospital B-I	Survival	79.9%	68.8%	62.9%	47.2%	23.6%
	n. risk	61	37	14	5	1
	std. err	0.04	0.05	0.06	0.11	0.17

The primary aim of this research was not to compare migration rates, either proximal or distal, between participating centres. These data are available but must be treated with caution, since there is a wide range in the number of patients included by each of the participating centres (Table 6.15 and Table 6.16). Between centres, the proximal migration rate ranged from 0 to 44%. Based on the evidence available and when using a Chi-squared test these differences between centres did not reach statistical significance (P=0.05). Distally, the range was narrower (0 to 29%) but again when using a Chi-squared test, there was no statistical significant (P=0.34). In both of these situations the Chi-square test must be used with some caution as there were lower frequencies for some participating centres. As Frankfort-Nachmias and Leon-Guerrero report, Chi-square is sensitive to small expected frequencies in the cells and caution needs to be taken when in interpreting Chi-square if one or more cells have frequencies less than 5 (Frankfort-Nachmias and Leon-Guerrero, 2010). All institutions participating in this study are high volume UK vascular centres. Training for FEVAR was supervised by a single manufacturer (Cook Medical Inc), proctoring was provided clinicians from Hospital A, who were first to undertake FEVAR within the UK.

Table 6.15 Migration distances and event timings for proximal migration for individual participating centres.

Centre	A	B	C	D	E	F	G	H	I
Patient	**n=60**	**n=22**	**n=16**	**n=14**	**n=14**	**n=12**	**n=9**	**n=4**	**n=3**
1	9.6 mm [24.2 mo]	4.1 mm [9.0 mo]	6.7 mm [11.8 mo]	5.3 mm [7.4 mo]	4.3 mm [13.6 mo]	6.8 mm [9.0 mo]		4.3 mm [9.3 mo]	
2	4.6 mm [54.9 mo]	4.8 mm [6.0 mo]	4.1 mm [17.9 mo]	4.8 mm [4.4 mo]		7.7 mm [2.0 mo]			
3	8.5 mm [37.2 mo]	10.0 mm [7.0 mo]	5.0 mm 22.6 mo]	4.4 mm [6.0 mo]		5.1 mm [48.1 mo]			
4	9.5 mm [44.6 mo]	8.0 mm [12.8 mo]	8.6 mm 11.0 mo]	7.0 mm [18.5 mo]		7.5 mm [10.8 mo]			
5	7.8 mm [11.7 mo]		4.6 mm [9.9 mo]	9.8 mm 16.2 mo]					
6	9.0 mm [9.2 mo]		6.6 mm [21.5 mo]	4.2 mm [6.0 mo]					
7	6.0 mm [12.0 mo]		4.3 mm [11.5 mo]						
8	5.0 mm [52.9 mo]								
9	4.3 mm [88.7 mo]								
10	6.0 mm [24.5 mo]								
Total	10 (17%)	4 (18%)	7 (44%)	6 (43%)	1 (7%)	4 (33%)	0 (0%)	1 (25%)	0 (0%)

Values presented are the caudal migration distance in millimetres, values within the parentheses indicate the migration event time (1st CT diagnosis). Pearson Chi-Square test *P*=0.05. Mo, months.

Table 6.16 Migration distances and timings for distal (iliac limb) migration for individual participating centres.

Centre	A	B	C	D	E	F	G	H	I
Limb(s)	n=110	n=33	n=28	n=22	n=27	n=16	n=13	n=6	n=6
1	*Contra* -7.2 mm [38.0 mo]	*Ipsi* -4.7 mm [6.0 mo]	*Ipsi* -11.9 mm [11.0 mo]	*Contra* -13.2 mm [6.0 mo]	*Contra* -4.6 mm [23.0 mo]		*Ipsi* -5.4 mm [12.0 mo]		
2	*Contra* -5.5 mm [89.0 mo]	*Contra* -6.5 mm [7.0 mo]	*Ipsi* -6.0 mm [23.0 mo]	*Ipsi* -6.0 mm [38.0 mo]					
3	*Contra* -6.0 mm [12.0 mo]	*Ipsi* -7.2 mm [25.0 mo]	*Contra* -15.6 mm [24.2 mo]	*Ipsi* -5.0 mm [6.0 mo]					
4	*Ipsi* -21.3 mm [37.0 mo]	*Ipsi* -5.2 mm [12.0 mo]							
5	*Ipsi* -7.4 mm [10.0 mo]	*Ipsi* -5.8 mm [20.0 mo]							
6	*Ipsi* -8.6 mm [5.0 mo]								
7	*Ipsi* -4.3 mm [14.0 mo]								
8	*Contra* -6.4 mm [23.0 mo]								
9	*Contra* -17.8 mm [49.0 mo]								
10	*Contra* -11.2 mm [5.0 mo]								
11	*Contra* -5.0 mm [35.0 mo]								
12	*Contra* -6.4 mm [36.0 mo]								
13	*Contra* -5.5 mm [13.0 mo]								
14	*Contra* -6.0 mm [6.0 mo]								
15	*Ipsi* -6.6 mm [63.0 mo]								
16	*Ipsi* -7.8 mm [27.0 mo]								
17	*Ipsi* -4.4 mm [41.0 mo]								
Total	17 (15%)	5 (15%)	3 (11%)	3 (14%)	1 (4%)	0 (0%)	1 (18%)	0 (0%)	0 (0%)

Values presented are the cranial migration distance in millimetres, values within the parentheses indicate the migration event time (1st CT diagnosis). Pearson Chi-Square test *P*=0.39. Mo, months.

6.3.7 Progression of migration

The issue of the stability of a device following migration is often raised within the vascular community. Do migrated stent-grafts continue to migrate or do they migrate into a more stable position and no further movement is seen? For proximal migration there is much discussion around the issue of barb engagement. Is some initial (minor) movement expected whilst the anchoring barbs engage into the aortic wall? Based on data included in this chapter, fifteen patients (45%) with proximal migration were diagnosed at the last follow-up CT scan. Of the remaining 18 (55%) patients, there was a small amount of further movement (mean +1.0, SD 1.8, range -2.4 to +4.6 mm) over a median 21 (IQR 10.6 to 28.5, range 1 to 80) months of remaining follow-up.

For patients with distal (iliac) limb migration 41 limbs demonstrated CT evidence of migration. Nineteen (46%) limbs were diagnosed as migrated on the last follow-up CT scan. Of the remaining 22 (54%) limbs there was further movement (mean -2.0, SD 1.9, range -6.1 to +0.7 mm) over a median 16.5 (IQR 12.0 to 28.3, range 4 to 64) months of further follow-up. Full details of the progression of distal iliac limb migration (between limb types) are described in Table 6.17.

Table 6.17 Progression of iliac limb migration after reaching criterion (≥ 4 mm)

		All limbs	Ipsilateral	Contralateral
Migrated limbs, n		41	19	22
Migrated at last follow-up, n		19 (46%)	9 (47%)	10 (45%)
Limbs with additional movement, n		22 (54%)	10 (53%)	12 (55%)
Additional migration, mm	Mean	-2.0	-2.8	-1.4
	SD	1.9	1.9	1.7
	Minimum	-6.1	-6.1	-5.1
	Maximum	+0.7	+0.1	+0.7
Further follow-up time, months	Median	16.5	16.5	16.5
	IQR, 1st quartile	12.0	12.3	12.0
	IQR, 3rd quartile	28.3	28.8	26.8
	Minimum	4.0	4.0	7.0
	Maximum	64.0	63.0	64.0

SD, standard deviation. IQR, inter-quartile range. Percentages, indicated by parentheses, are based on the total number of migrated iliac limbs per column.

6.4 Discussion

Aortic stent-graft technology is dynamic and ever-changing. The constant challenge for the endovascular community is to develop devices which lead to a decrease in complications and whilst allowing the safe treatment of more complex aneurysms (Stokmans *et al.*, 2012). Just over a decade ago, fenestrated aortic stent-grafts were such a development and have extended the role of EVAR to include complex AAA. Many patients, who previously would have been excluded from open repair or standard EVAR, now have the option of treatment.

Early enthusiasm for a technology does not necessarily translate into to improved outcomes. There are continual pressures amongst clinicians to continue to widen inclusion criteria and treat more complex aortic disease. This approach must be taken with caution, Schanzer *et al.*, in 2011 identified a link between the treatment of infrarenal AAA outside of the manufacturers IFU (more complex disease) and post-EVAR aneurysm expansion. FEVAR is now a well-established technique, more than 3000 patients have been treated and this trend is growing at an exponential rate (Amiot *et al.*, 2010). Concerns still exist that endovascular techniques have unacceptably high complication and reintervention rates (BSET and GLOBALSTAR Collaborators, 2012). There have also been reports of the occasional late rupture following EVAR (Harris *et al.*, 2000, Wyss *et al.*, 2010, Schlosser *et al.*, 2009). With FEVAR devices, stent-graft migration has been associated with serious complications including target vessel loss (Verhoeven *et al.*, 2010) and type 1 endoleak (Troisi *et al.*, 2011). There is also growing speculation regarding its role in post-FEVAR rupture.

Based on multicentre data presented in this chapter, proximal migration was identified in 33 of out 154 patients (21%). Kaplan-Meier survival analysis, using interval censoring, estimated the incidence of proximal fenestrated stent-graft migration to be 18%, 23% and 36% at 12, 24 and 48 months, respectively. According to KM methods, the greatest incidence of proximal migration was during the first 12 months following implantation. Unlike the single centre series within the previous chapter, there were only small differences in migration estimations between the four event time definitions used. The greatest difference was at 48 months and between the interval censoring and beginning of the interval event times. In this situation using the beginning of the interval caused an underestimation of migration by 7%. When compared to the single centre data (Chapter 5),

the migration rate was initially higher for the multicentre cohort at 12 months (18% versus 9%), this equalised by 36 months (23% versus 22%) but then again increased in the multicentre cohort by 48 months (36% versus 22%). By using data from the larger cohort it can be concluded that proximal migration occurs in around one third of patients by 4 years. There appears to be an initial peak in migration, which occurs during the first year, this could be explained by movement associated with engagement of the anchoring barbs in the aortic wall. This theory was discussed by Zhou *et al.*, in their lab based experiment (Zhou *et al.*, 2007). Zhou and colleagues, investigated the forces required to cause migration in standard and a stent-graft with a single fenestration. Their report identified an initial phase of movement (barb engagement) following by a period of stability and then a second phase of movement. The 13% rise in migration from 36 to 48 months may correlate with this second phase of migration. It is, however, clear from both multicentre data and reports within the literature that proximal migration can occur at any time point during follow-up.

Distally (iliac) limb migration occurred in 34 out 259 limbs (13%) and was seen in 15%, 18% and 35% of patients by 12, 24 and 48 months, respectively. When compared with the single centre analysis (Chapter 5), migration rates were lower 5%, 14% and 30%, respectively. The greatest difference in migration rates (10%) was at 12 months. Differences in sample size could explain this. An alternative explanation could be that more individual limbs were available for assessment in the multicentre cohort thus increasing the probability of migration. However, arguing against this were the relatively equal ratios of iliac limbs assessed in the single centre report (98 out of a possible 110 limbs, 89%) and the multicentre cohort (259/290, 89%). Limb-by-limb analysis demonstrated similar instances of migration regardless of limb type in the multicentre cohort. At 12 months, iliac migration was

experienced in 5% of individual limbs and this increased to 24% by 48 months. For both limb types the greatest incidence of migration was between 24 and 36 months (12% to 14%). There are two explanations to explain this trend, firstly, there are a lack of fixation mechanisms for iliac limbs when compared to the proximal device (target vessel stents, anchoring barbs). There are also smaller forces acting on the iliac limbs when compared to the proximal main body. Migration of the iliac limbs is, therefore, likely to be a slower process. Adding to this is the possibility that iliac limb fixation may deteriorate (radial force) over time in some patients if there is progressive iliac limb dilatation. This is likely to be a relatively slow process and this may be a reason for seeing a later spike in iliac limb migration.

Data presented within this chapter sought to briefly compare migration outcome data between the single (pilot) centre (Hospital A) and the multicentre cohort (Hospitals B – I). Broadly patients from Hospital A and B-I were comparable in terms of baseline criteria. There was, however, a significantly longer follow-up duration for patients from Hospital A. This difference has been previously explained in that Hospital A was the first UK centre to embark on FEVAR procedures. As a result the overall follow-up duration for this cohort was longer as procedures had started earlier. It is also likely that some of the initial patients treated at Hospital A may have been treated with less complex AAA morphologies (e.g. a single unstented renal fenestration). This may provide some explanation as to the differences in the stent-graft configurations and proximal migration rates between the two cohorts. By way of an example by 24 months an additional 15% of patients were free from proximal migration at Hospital A when compared with Hospitals B – I (Figure 6.17). When

comparing the actual proximal migration distances between the two cohorts they were similar (*P=0.167*).

Iliac limb migration distances were also similar between the two cohorts (Figure 6.18 & Figure 6.20). Time to 1st CT diagnosis of migration had a tendency to be longer for patients at Hospital A. This latter point may again reflect the longer median follow-up duration for patients within this cohort. When comparing Kaplan-Meier estimates, freedom from any iliac limb migration was similar between the two cohorts (P=0.53). Breakdown of migration events by limb type (ipsi- versus contralateral) revealed, based on the available evidence, no statistically differences between the two cohorts (P>0.05). Further analyses revealed no statistically significant differences in the incidences of a proximal and at least one distal iliac migration (P=0.23) or any proximal or distal migration event (P=0.71). Visual inspection of the survival curves for all analyses was undertaken, findings were again consistent with the reported p values. Comparison between the two cohorts (Hospital A versus Hospitals B – I) relied heavily on the use of survival analyses with an interval censoring approach. The choice of event time definition and survival analysis approach has been the subject of further analysis and discussion. It is fair to acknowledge that if different event time definitions were used then there could be some differences in the estimations of freedom from migration when comparing cohorts. A full analysis of this issue for each cohort was beyond the project time frame.

When consider the overall multicentre cohort (n=154) the magnitude of migrations was similar to those experienced in the single centre cohort (n=55), proximal migration median +6 mm, distal/iliac limb migration -6 mm). Of all the cases of migration which reached criteria (n=67, both proximal and distal), 42% were < 6 mm. Maximum proximal

migration was +10 mm in a caudal direction whereas the maximum iliac limb migration was -21 mm cranially. If referring to the stent-graft force diagram by Mohan *et al.*, in Chapter 3 (Mohan *et al.*, 2002), forces acting on the proximal device operate in the caudal direction whereas forces on the iliac limbs cause the device to migrate cranially. It is for this reason that within the literature several iliac limbs were reported to have migrated back into the aneurysm sac with an accompanying distal type 1 endoleak (Alerci *et al.*, 2005). In order to minimise distal type 1 endoleaks, iliac limbs should be deployed in a reasonably length of CIA or the device must be extended into the EIA. In this full multicentre cohort, the median (IQR) distance between the CIA bifurcation and the distal iliac limb were 16 (10 to 23) mm and 18 (9 to 25) mm for the ipsilateral and contralateral sides, respectively (data reported within the appendix). In addition, data from this chapter reporting the consistent deployment of the iliac limbs close to the CIA bifurcation may explain the low distal type I endoleak rate.

In the previous chapter it was identified that comparison of migration rates against those published in the literature is difficult. This is also the case for the multicentre data and the broad conclusion is that both the incidence and timings are in keeping with the limited information published within the literature. It must be highlighted that this study focused on identifying stent-graft migration using robust assessment methods and strict definitions. It is the first quantitative account of fenestrated stent-graft migration within the literature. There have been several discussions about prospective trials and the need to evaluate the newly available fenestrated devices (e.g. Ventana). Methods and data within this thesis will provide essential data for those comparisons.

The resultant effects of any fenestrated stent-graft migration must be considered. Three principle complications, which are potentially associated with migration, include graft-

related endoleaks, target vessel loss and rupture (Resch *et al.*, 2010). Causes of all of these complications are likely to be multifactorial. With regard target vessel loss, the preoperative quality of vessels, stent-graft selection, graft deployment and disease progression can all play a part (Scurr and McWilliams, 2007). For endoleaks, these can also depend on adverse aortic neck features, stent-graft design and deployment issues (Wain *et al.*, 1998). In order to make an informed decision as to whether a complication is related to migration would require carefully review of each individual case, often as part of a multidisciplinary team. When considering the cause of ruptures this is more complicated. For infrarenal EVAR devices, there are patients with untreated proximal type 1 endoleaks which who progressed on to rupture. There are also patients without any prior complications whose aneurysms proceeded to rupture (Wyss *et al.*, 2010). The report by Wyss et al., was based on data from the UK EVAR trials, five (18.5%) patients had a late rupture despite no adverse events during follow-up. All three of the FEVAR ruptures reported within the literature have been attributed either to type 1 or 3 (graft-related) endoleaks.

Using data from this chapter, if it was assumed that all type 1 and 3 endoleaks and target vessel losses in the proximal migration group resulted from migration then the clinical significant migration rate was 4.5%. This fits within the reported ranges (around 3%) of proximal fenestrated stent-graft migration within the literature (Table 2.4). With the regards the assessment of complications and reinterventions, the resultant log-rank tests demonstrated no differences in migration-related sequelae in patients with and without proximal migration. There are two further points to consider from the complications and reinterventions summary statistics (Table 6.10 and Table 6.11). Despite no apparent statistical significance (P=0.39), there were fewer late (> 6 weeks) type 2 endoleaks in the

proximal migration group (6%), when compared to patients without evidence of migration (14%). There is an *in vitro* study within the literature that has suggested that the downward displacement force on a stent-graft is lower in the presence of an endoleak (Li and Kleinstreuer, 2006b). If this theory is true, then the trend from this multicentre cohort provided some clinical evidence of low migration rates in the presence of endoleak. There was also a non-statistically significant difference (P=0.12) in endograft kinking rates between patients with (15%) and without (7%) proximal migration. This is perhaps unsurprising, if a device moves caudally and there is an absence of space for it to move into, then it will buckle or kink. For infrarenal stent-grafts the EUROSTAR report, by Fransen and colleagues, demonstrated an association between kinking and stent-graft migration (Fransen *et al.*, 2003a).

With the low rates of iliac limb occlusion and distal type 1 endoleaks, iliac limb sequelae was not investigated in further detail. This fits in with the literature, where there is a lack of detailed reports investigating associated complications from the migration of an iliac limb. Reasons for this could be similar, there could be a lack of complications relating to iliac limb migration or there could be a lack of awareness that iliac limbs can migrate. It is worth noting that the follow-up duration in the cohort reported in this chapter, at best, may only be considered to cover the medium term. It is possible that there could be a spike in the incidence of iliac migration and related events when patients are subjected to more long-term follow-up. It is for this reason that patients should be followed up over the long-term (up to 10 years) and events reported as part of a prospectively designed trial or submitted through a registry. The UK EVAR trial has studied patients out to 10 years and although did

not provided specific details of individual complications did report that new complications were still be reported after 8 years (Greenhalgh *et al.*, 2010).

Low incidences of fenestrated stent-graft migration and minimal related sequelae could be attributed to the design of the fenestrated stent-graft. Standard (infrarenal) stent-grafts achieve a seal using a section of normal aorta below the most caudal renal artery. Device fixation varies by manufacturer, but is often a combination of radial force, longitudinal columnar support and barbs which embed into the aortic wall. Fenestrated stent-grafts are similar but have the addition of fabric coverage above the caudal renal artery. In many instances, the fabric will extend up to or above the origin of the SMA. Nowadays, the majority of fenestrated stent-grafts also have target vessel stents which provide further fixation within the aorta. Further resistance to proximal migration may be achieved using a separate distal bifurcated component. The aim of a separate proximal and distal component is to focus the displacement forces that act on the aortic bifurcation on to the distal component, thereby preventing proximal movement (Dowdall *et al.*, 2008). Dowdall and colleagues investigated the separation of the modular components of the Zenith fenestrated AAA stent-graft. In their series of 106 patients, 14 (13%) had evidence of movement between the proximal and distal bodies (≥ 10 mm). This indicates that the distal bifurcated body does directing some of the downward displacement force away from the proximal component. The significance of inter-modular component separation in preventing migration will be considered in the next chapter. The Zenith fenestrated AAA endograft also uses the same barb fixation system used in the conventional infrarenal Zenith device. In a US multicentre trial (n=739), spanning over 5 years only 19 (2.6%) patients showed evidence of

stent-graft migration (5 - 10 mm) and this was largely attributed to the barb fixation system (Greenberg *et al.*, 2008).

With the data reported in this chapter, there are cases of proximal and distal migration where the displacement force on the stent-graft exceeded its fixation. Within Chapter 2 of this thesis, the factors affecting the displacement force were discussed and the resistive mechanisms of a stent-graft against migration identified. Of the 33 patients with proximal migration the individual circumstances surrounding each case could be evaluated and compared against a subgroup without any migration. It is perhaps more sensible to use the incidence of migration together with data from the available preoperative and postoperative variables in order to produce a more scientific and rigorous evaluation of the causative factors of migration. This work has been presented in the next chapter.

Limitations

When considering the reported incidence of migration in this chapter the impact of any missing patients must be considered. Out of the possible 262 patients 154 (59%) were included in this analysis. Questions must arise as to whether there is stent-graft migration and or its associated complications within the 108 patients unavailable for analysis. If so, the inclusion of these patients may have contributed to a different migration rate than has currently been reported within this chapter. With standard infrarenal stent-grafts device migration has been associated with post-EVAR rupture (Wyss *et al.*, 2010, Harris *et al.*, 2000) and the need for open conversion (Harris *et al.*, 2000). Some commentators would expect to see an incidence of post-FEVAR rupture and possibly a similar relationship to stent-graft migration. Whether there could be incidences of post-FEVAR migration-related rupture in

the excluded patient group must also be considered. The lack of any post-FEVAR ruptures in the included cohort is highly encouraging and there are possible reasons to explain this. For standard infrarenal EVAR post-treatment rupture has been experienced in approximately 0.6% (Harris *et al.*, 2000) to 3.2% of patients (Wyss *et al.*, 2010). From the current publications reporting FEVAR outcomes (patients, n=819), there have been post-treatment ruptures in only 3 (0.4%). In each case, rupture was attributed to either a type 1 or type 3 endoleak with timings at 5 days, 10 months and 18 months (Bicknell *et al.*, 2009, Metcalfe *et al.*, 2012, Ziegler *et al.*, 2007). These reports confirm that there is a low risk of post-FEVAR rupture and this can occur early or late during follow-up. With 154 patients included in this analysis, rupture rates of 0.4% rate would suggest that approximately one case could be expected within this multicentre cohort. Further detail on the three reported cases would be needed in order to confirm that they had similar characteristics to the multicentre cohort reported in this chapter (e.g. AAA diameter, follow-up, management of complications etc). With specific regard to excluded patients, this was due to an inability to access the necessary imaging data. These patients had been included in the GLOBALSTAR registry and its resultant publication in 2012 (BSET and GLOBALSTAR Collaborators, 2012). This was, however, the first publication from the GLOBALSTAR registry and median follow-up was only short (6 months). This core lab review of FEVAR migration followed initial the GLOBALSTAR report and, therefore, contained more long-term follow-up data (median 20.9, IQR 10.4 to 36.5 months). The possibility of migration and or a low incidence of post-FEVAR rupture in excluded patients must be considered when interpreting these results.

Other considerations within this chapter are any differences in the baseline characteristics between the included and excluded patients. Theoretically, it is possible that

there could be differences in the incidence of migration between included and excluded patients. With an absence of any risk factors for fenestrated stent-graft migration, it was difficult to compare and conclude that both groups were similar. In view of the number of exclusions, attempts have been made to compare groups based on the available baseline characteristics. Age, gender and maximum preoperative AAA diameter were not found to be statistically different between groups. Questions may arise as to whether these three variables are sufficient to state that both groups are comparable. Age and gender are typically described for vascular surgical cohorts and there are also reports documenting a relationship between AAA diameter and neck angle and length (Zhang et al., 2001). Based on this publication AAA diameter could be used as a surrogate marker aortic neck complexity. If AAA diameters were relatively similar then it could be suggested, based on the report by Zhang et al., that the morphologies of the aortic neck are likely to be similar. Such an assumption is important since several risk factors for infrarenal stent-graft migration are based on preoperative aortic neck morphology (Chapter 3).

There are further limitations regarding the retrospective use of multicentre data. Firstly, there are likely to be some variations in preoperative imaging, patient selection, implantation procedure and aftercare between institutions. Such variation is likely to be minimal as all centres fall under a single healthcare system (UK National Health Service), procedures are performed under the supervision of a single manufacture (Cook Medical Inc) and training and mentorship was provided by the first centre to start this procedure in the UK (Hospital A). If this were an international multicentre study, then there could be geographical variations in the incidence of comorbidities (e.g smoking or hypertension). Surgical techniques could have slight differences and so could postoperative care. In these

situations it is desirable to undertake any analyses using clustering methods. The assumption of any cluster analysis is that the objects within a cluster are in some sense more similar to each other than objects in other subgroups (Shannon, 2008) and that observations in a cluster tend to be correlated (Petrie and Sabin, 2009). Failure to acknowledge this correlation may result in the underestimation of standard errors. The majority of work within this thesis is based on an assessment of CT data at the study institution by a single observer. The use of a single observer in a centralised location will remove some of the issues surrounding clustering. Also, from a statistical point of view, cluster analysis requires a minimum number of individuals (or objects) per cluster, and in this study there were centres with insufficient samples sizes to fit a meaningful model which would take into account correlations within centres.

There were several missing iliac limb migration measurements when there was a CT image quality issue or a non-patent IIA. In these CIAs there were iliac limbs present which could have migrated. The majority of KM data presented refers to a subgroup of patients, where missing iliac limb assessments have been excluded from the analysis. To explore the impact of excluding these data, two sensitivity analyses have been undertaken. The first analysis assumed that all of the originally non-assessed limbs had migrated by the 6-month CT scan and that there was a 1-month interval CT scan present. The second scenario, assumed that any non-assessed limbs had migrated with a similar incidence/timing to those observer in the multicentre cohort, where a full CLL assessment was possible. For the 1st scenario modifying the dataset had little effect on migration rates for the ipsilateral limb but increased the incidence of contralateral limb migration by between 12% and 16% across each of the time points. For the second scenario, the incidence of migration between the original

and the modified datasets were almost equal. When interpreting the iliac limb migration data, it is important to consider that some of non-assessed limbs may have migrated. It is also important to consider that one of the main reasons for not assessing an iliac limb was occlusion of the IIA. It is not clear how an occluded IIA would affect the overall flow dynamics and whether this could have an effect on the incidence of iliac limb migration. If alternative migration measurement techniques were available and validated then this could be researched.

6.5 Conclusion

Migration at the proximal landing zones occurs in around a third of patients by four years. The incidence of proximal migration peaks twice, once during the first year after repair and a second between years 3 and 4. Proximal migrations were all caudal in direction and the majority (60%) were less 6.9 mm in length. Clinical sequelae were infrequent with no statistically significant differences between complications and reinterventions were identified in patients with and without proximal migration. Freedom from any iliac limb migration showed a similar incidence to proximal migration. The incidence peaked between years 2 and 3 and a third of patients had at least one iliac limb migration by 4 years. Overall, iliac related complications and reinterventions were rare. Proximal migration does not appear to be significantly associated with proximal type 1 endoleak or target vessel loss. Concerns still exist regarding any post-EVAR rupture and any association with migration. Ruptures have been reported for FEVAR and since migration can occur at any time point routine follow-up imaging still is recommended.

7. Predictive factors for proximal migration

7.1 Introduction

Previous reports have identified anatomical, procedural and device-specific factors that have been associated with stent-graft migration (Cao *et al.*, 2002, Arko *et al.*, 2005, England *et al.*, 2004, Mohan *et al.*, 2002). Such reports are, however, predominantly limited to investigations involving standard (infrarenal) aortic stent-grafts. It is accepted that any attempts to identify predictive factors for fenestrated stent-grafts, would also be advantageous. If there are associations between fenestrated stent-graft migration and pre- or post-operative variables then 1) high risks patients could be excluded from treatment, or 2) for those who are treated and at high risk they could be followed-up more closely or have follow-up tailored to their individual risk profile. There could also be benefits for device manufacturers, a greater understanding of risks factors could help direct future modifications to stent-grafts.

Movement of a fenestrated stent-graft at the proximal landing zone is potentially disastrous and could result in a significant target vessel loss or reperfusion of the aneurysm, with the possibility of rupture. All three cases of post-FEVAR rupture reported in the literature had a graft-related endoleak (Bicknell *et al.*, 2009, Metcalfe *et al.*, 2012, Ziegler *et al.*, 2007). There is a general consensus within the literature that the potential consequences of proximal migration of both fenestrated and convention (infrarenal) stent-grafts are considered to be more serious that distal (iliac) limb migration. It is for this reason that the investigation of predictive or risk factors for fenestrated stent-graft migration will focus on proximal landing zone.

7.1.1 Aims

Within the last chapter, multicentre data were presented outlining the incidence, timings and related sequelae for migration of the Zenith fenestrated AAA stent-graft. As part of this retrospective data collection process, a series of pre-, intra- and post-operative variables were collected from the GLOBALSTAR registry, locally available databases and from direct measurements from CT scans. These variables formed the basis of the predictive factor analysis. Using these variables the aims of this chapter are as followed:-

Aim 7.1. To establish the risk factors for proximal migration of a Zenith fenestrated aortic stent-graft.

Aim 7.2. To identify any protective factors for proximal migration of a Zenith fenestrated aortic stent-graft.

Aim 7.3. To investigate and report the magnitude of effect for any identified risk or protective factors that are associated with proximal fenestrated stent-graft migration.

In order to undertake a successful predictive factor analysis, a review of the literature was essential. All variables that have been investigated for possible association with stent-graft migration were identified. Many of these have been identified and discussed within the introductory chapters (2 & 3). For simplicity, these have also been summarised in the table below (Table 7.1). When considering these factors there are some limitations since, almost all were acquired either using lab-based experiments or clinical data from patients with conventional (infrarenal) stent-grafts implanted. To the author's knowledge, only two studies, have explored the relationship between potential risk factors and the migration of a

fenestrated stent-graft (Scurr *et al.*, 2008b, Zhou *et al.*, 2007). Both of these studies were lab-based experiments and undertaken more than five years ago. The study by Zhou and colleagues investigated the additional distraction force needed to displace fenestrated graft incorporating a single target vessel stent, when compared to a standard infrarenal device (Zhou *et al.*, 2007). In their report Zhou *et al.*, confirmed that a device with a single stented fenestration does offer higher ultimate fixation. The publication by Scurr and colleagues, from the same institution, compared the forces needed to crush different types of target vessel stents when subjected to distraction forces (Scurr *et al.*, 2008b). Scurr's report evaluated three target vessel stents (Jostent, Advanta V12 and Palmaz Genesis) and concluded that there were no significant differences in the ability of either stent to withstand a crushing force when deployed within an endograft fenestration.

Table 7.1 Previously investigated risk factors for aortic stent-graft migration (n represents the sample size)

Risk factor	Author(s)	Year	n	P value
Increase in aortic neck diameter	Cao *et al.*	2002	148	0.01
	England *et al.*	2004	38	NS
Preoperative AAA diameter	Cao *et al.*	2002	113	0.02
	Mohan *et al.*	2002	2862	0.01
	England *et al.*	2004	38	NS
Proximal graft diameter	Mohan *et al.*	2002	2862	0.01
	Cao *et al.*	2002	113	NS
Aortic neck angulation.	Cao *et al.*	2002	113	NS
	England *et al.*	2004	38	NS
	Wyss *et al.**	2011	217	0.08
Aortic neck length.	Cao *et al.*	2002	113	NS
	England *et al.*	2004	38	NS
	Waasdrop *et al.*	2009	154	0.001
Aortic neck thrombus.	Cao *et al.*	2002	113	NS
	Wyss *et al.**	2011	217	0.02
Aortic neck calcification.	Wyss *et al.**	2011	217	0.04
Distal transverse aortic neck diameter	Mohan et al.	2002	2862	0.02
Renal artery to stent-graft distance	Zarins *et al.*	2003	1119	<0.01
	Waasdorp *et al.*	2009	154	<0.001
	Heikkinen *et al.*	2006	173	<0.01
Endoleak at 30-days.	Cao *et al.*	2002	113	NS
Graft oversizing	Cao *et al.*	2002	113	NS
	Mohan *et al.*	2002	2862	NS
Device type, bifurcated versus AUI	Waasdrop *et al.*	2009	154	0.01
	Mohan *et al.*	2002	2862	NS
Smoking	Mohan *et al.*	2002	2862	0.02
Hypertension	Mohan *et al.*	2002	2862	0.04
Heart rate	England *et al.*	2004	38	0.03
Stiff body device	Cao *et al.*	2002	113	NS
Iliac artery engagement distance	Arko *et al.*	2005	8	<0.001
	Heikkinen *et al.*	2006	173	<0.001
	Waasdorp *et al.*	2009	154	<0.001
Presence of proximal barbs	Malina *et al.*	1998	137	<0.001
Pulsatile aortic neck distension	Van Keulen *et al.*	2010	26	0.03

*the paper by Wyss *et al.*, covered generic EVAR complications and not specifically migration. NS: not significant.

7.2 Materials and methods

7.2.1 Patient Data

The inclusion criteria have been previously discussed in Chapter 6. A total of 262 patients were potentially available and of these 154 (59%) satisfied the inclusion criteria and received a subsequent CT CLL assessment of proximal migration. Differences in study entry parameters, between the included (n=154) and excluded (n=108) groups have been previously compared (see Section 6.3.1). Limited data were available from the excluded patients and essentially there were no statistically significant differences in the age, gender and preoperative AAA diameters between the two groups (P>0.05).

To summarise, key data from the previous chapter, based on an analysis of 154 patients with a median 20.9 (IQR 10.4 to 36.5, range 6 to 109) months follow-up, proximal migration was experienced in 33 (21%) patients. Kaplan-Meier survival analysis, using an interval censoring approach, estimated freedom from proximal migration (where proximal migration is defined as movement ≥ 4 mm) of 82%, 77% and 77% at 12, 24 and 36 months, respectively.

A series of preoperative, intra- and postoperative variables were collected from CT scans, local endovascular databases and the GLOBALSTAR registry. A list of collected variables and their relevant definitions have been provided (Table 7.2) (Appendix). Definitions were taken from the relevant reporting standard, previous journal articles or consensus opinion within the research team. All direct CT measurements were undertaken by the author following appropriate training, using a departmental PACS workstation, which had an in-built vessel analysis module (Kodak Carestream PACS, 10.2, Kodak, Rochester, NY).

The author has been previously involved in several research studies which have used CT based measurements to evaluate outcomes and complications following EVAR and FEVAR (England et al., 2004, Wyss et al., 2009, England et al., 2010b, England et al., 2008, England et al., 2010a, Oshin et al., 2010). Part of these studies involved the assessment of intra- and inter-observer variability.

Table 7.2 Variables collected within this retrospective multicentre review.			
Baseline (preoperative) variables			
Continuous variables	*Categorical variables*		
Age, years	Gender	Chronic renal insufficiency	
Body mass index, kg/m^2	Smoking status	Diabetes mellitus	
Heart rate, b.p.m	Ischaemic heart disease	ASA physical grade	
Systolic blood pressure, mmHg	Heart failure		
Serum haemoglobin, g/dL	Hypertension		
Graft-related variables			
Continuous variables	*Categorical variables*		
Stent-graft diameter, mm (proximal)	Graft shape (bifurcated, AUI or tube)		
Stent-graft length, mm (proximal body)	Target vessel configuration (number, type, stented or unstented).		
MDCT CTA variables	CT time point		
*Continuous variables (*mm unless otherwise stated*)*	Preoperative	1st postoperative	Subsequent follow-up
Aortic diameter at the middle of the:			
CA, SMA, CrRA, CaRA & BN	✓	✓	✓
Maximum diameter of the:			
AAA, CIA	✓	✓	✓
Vessel length from:			
CA to SMA; SMA to CrRA; CrRA to CaRA; CaRA to BN; BN to aortic bifurcation; Aortic bifurcation to CIA bifurcation.	✓	✓	✓
Angulation of:-			
Maximum coronal aortic neck (°)	✓	✓	✓
Maximum sagittal aortic neck (°)	✓	✓	✓
Graft-related measurements			
SMA to proximal stent-graft		✓	✓
CIA to ipsi- & contralateral limb		✓	✓
CA to distal bifurcated component		✓	✓
Ipsilateral limb diameter (stent)		✓	✓
Contralateral limb diameter (stent)		✓	✓
Categorical variables			
Vessel patency		✓	✓
Endoleak		✓	✓
Kinking		✓	✓
Component fracture		✓	✓

In order to investigate the risk factors for proximal migration of fenestrated stent-grafts a series of statistical analyses were undertaken.

7.2.2 Statistical analysis plan

In order to satisfy the aims of this chapter (Aims 7.1, 7.2 and 7.3) the demographic, clinical, anatomical and graft-related features of patients with CT evidence of proximal stent-graft migration were compared to those without any evidence of migration. Analysis then comprised of a series of univariate and multivariate statistical techniques.

Describing the study cohort

Firstly, a selection of appropriate summary statistics were presented for all variables. At this point there were no subgroupings according to proximal migration status. The majority of variables were captured from the GLOBALSTAR registry or using direct measurements from CT scans. Within the summary statistics there were brief descriptions of any missing values. For continuous variables, the distribution of the data was first assessed using the Shapiro-Wilk normality test (Shapiro and Wilk, 1965). Next, appropriate summary statistics were presented, for data that were approximately normally distributed, the mean plus or minus its standard deviation were reported. For those variables that had a non-normal distribution, the median values with their respective inter-quartile ranges were stated.

Analysis of missing values

The second phase of the statistical analysis was to compare the frequencies of missing values between those patients with and without evidence of proximal fenestrated stent-graft migration. In order to do this, proximal migration was considered as a dichotomous variable (migration $\geq$ 4 mm). Included variables were coded as present or missing, differences in the frequencies of missing values for patients with and without proximal migration were then

described using absolute values and percentages. Differences were further assessed for statistical significance using Fisher's exact test.

Further consideration to the missing data was also given. According to Rubin, missing data can be classified as either missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR)(Rubin, 1976). Missing data are an important issue, the absence of data can be informative, and as Fielding *et al.*, stated, ignoring patterns of missingness may bias the results obtained (Fielding *et al.*, 2009). Understanding the precise mechanism regarding the missing values is useful as it can direct the most appropriate form of analysis. According to Fielding and colleagues complete-case analysis will only be unbiased if the data are MCAR (Fielding *et al.*, 2009). A number of hypothesis tests have been suggested that can be carried out to test for MCAR. Little, in 1988, developed a test that has become extremely popular and is based on the means under the different missing data patterns (Little, 1988). Other authors have also proposed an MCAR test based on mean values (Listing and Schlittgen, 1998). One of the first procedures to be undertaken when assessing missing values is to compare the distributions of the fully observed values for respondents and nonrespondents (Little, 1988). This test was described in the first paragraph of this section and was completed for all data variables analysed within this chapter. Little's MCAR test was also undertaken on all of the variables collected within this chapter. Little's MCAR test is based on the premise that under MCAR at each assessment the calculated means of the observed data should be the same irrespective of the pattern of missingness. The null hypothesis is that the data are MCAR.

Exploratory (univariate) analyses

Following the assessment of missing values, the next phase of the statistical analysis was the identification of risk factors using univariate analyses. The purpose of the univariate analyses were two-fold, 1) it can provide an indication of risk factors in its own right but 2) it can help guide which variables should be included in the multivariate analysis. For the univariate analysis proximal migration was treated as a binary variable (No migration = 0, proximal migration ≥ 4 mm = 1). All variables identified in Table 7.2 were grouped into their respective proximal migration and no migration subgroup. The type of the variable (continuous or categorical) and the distribution of the data informed the appropriate univariate statistical test to be applied (Table 7.3).

Table 7.3 Methods of univariate statistical analysis

	Data distribution	
Variable type	**Normal**	**Not normal**
Continuous	*t test*	Mann Whitney U test
Categorical (binary)	Fisher's exact test/ Chi-squared test	
Categorical (ordinal)	Chi-square test (including linear trend test)	

For the purposes of the univariate data analysis *P* values <0.05 were considered statistically significant, however, *P* values <0.1 were highlighted as they would be considered for inclusion in the subsequent multivariate analysis.

Multivariate analyses

For the multivariate analysis a Cox proportional hazards model was used. Time-to-event curves analysed by Cox proportional hazards regression are commonly used to describe outcomes in clinical studies. This methodology, as reported for example by Spruance *et al.*, has the advantage of using all available information, including whether the event has occurred, in addition to the timing of the event (Spruance *et al.*, 2004). Within this chapter, the survival data were modelled for all four event time definitions. As a reminder, these definitions included the beginning, the midpoint, the end of the interval (or time of 1st CT diagnosis of migration) and the interval censoring approach (See section 5.2.5). Variables achieving a $P<0.10$ in the univariate analysis were considered for entry into the multivariate analysis. The Cox proportional hazards model, a regression method for survival data, provides an estimate of the hazard ratio (HR) and its confidence interval for each of the factors included in the model (Spruance *et al.*, 2004). The hazard ratio as an estimate of the ratio of the hazard rates between two levels of explanatory variable (e.g. males versus females, 70-years old versus 80-years old). The hazard ratio is the probability that, given the event in question (migration) has not already occurred, it will occur in the next time interval, divided by the length of that interval. The time interval is made very short, so that in effect the hazard rate represents the probability (in this case migration) at a given time point. In this chapter the HR will be assessed to satisfy Aims 7.1, 7.2 and 7.3 and provide a statistical indication of risk/protective factors for proximal migration and an estimation of the strength of any association. A further consideration must by for any adjustments when dealing with missing data; these adjustments will be described later in the chapter.

Multivariate analysis requires carefully planning in order to achieve a robust analysis. Based on the experience of migration in this thesis (n=33) and a total cohort of 154 patients, consideration must be made on how many variables can be entered into a model. Several rules of thumb exist and some would argue that the analysis of risk factors associated with migration (where migration is treated as a continuous variable) should be limited to no more than eight covariates (20 patients per covariate). In logistic analysis, for example, when the outcome variable is binary (migration/no migration) the rule of thumb suggests that the number of explanatory variables in the model should be such that the number of events per variable is not lower than 10. There have been arguments made within the literature that this rule is too conservative and that fewer events per predictor can be used (Vittinghoff and McCulloch, 2007). The work by Vittinghoff and McCulloch (2007) is important in that for logistic and Cox regression they found situations where 5-10 events per variable were adequate to ensure validity of the analysis. For the analysis of data within this chapter, initially parameters were included in the multivariate model if they achieved a $P<0.10$ in the univariate analysis. A separate analysis will be conducted for those univariate variables with $P<0.05$. This method is considered to be a well-recognised statistical approach, it must always be clearly stated that the model was generated using stepwise regression and not specified in advance (Chatfield, 1995). In reality it is likely that different multivariate approaches, using Cox proportional hazards, will generate a series of models which must then be discussed and a decision on which was is likely to be most plausible made.

7.3 Results

7.3.1 Description of the cohort

Summary statistics were generated for a total of 154 patients without any subgrouping for proximal migration status. These summary statistics presented represent a cohort of patients in their later years of life (mean age 74 SD 7 years). The cohort also had the typical range of comorbidities, which is expected from those undergoing vascular surgery. Two-thirds of all patients had hypertension (84/127), a similar frequency were previous or current smokers (84/123). Overall ASA physical grading was 3 or more in 72% of patients (84/117). Aneurysm morphology typically reflected a group of patients with complex AAA. Preoperative CT scans were available in 95/154 (62%) patients. Reasons for fenestrated repair were not simply the absence of an infrarenal aortic neck, median (IQR) length of 7 (0 – 13) mm. Aortic neck angulation ranged from 0° to 85°, 8% of patients (8/95) had moderate or severe aortic neck calcification and 48% of patients (46/95) had moderate or severe aortic neck thrombus. Repair was predominantly using a bifurcated device, 143/154 (93%) and target vessel stents were present in at least one fenestration in 137/154 (89%) of patients. Of those patients where data was available, the mean proximal stent-graft diameter (n=83) was 29 (SD 4.5) mm. Median proximal component length (n=68) was 123 (IQR 109 to 137) mm. The table below provides detail on the summary statistics that are available, together with their respective location within the appendix (Table 7.4).

Table 7.4 Description of tables provided in the appendices summarising the full cohort of patients included in this chapter.

Appendix	Variables	Time point	Data type
APP_1	Demographic		Continuous
	Clinical	Preoperative /	
APP_2	CT AAA morphology	Intraoperative	Categorical
	Graft details		
APP_3	1st postoperative CT scan	<6 weeks following	Categorical
APP_4		implantation	Continuous
APP_5	Remaining follow-up CT	≥6 months following	Categorical
APP_6	scans	implantation	Continuous

The degree of missingness for each of reported variable varies depends on the parameter type and the data source e.g. registry or CT scan. A full analysis of missing values follows this section and carries an accompanying explanation as to the causes of any missingness.

7.3.2 Missing values analysis

Several of the variables collected within this study had values missing. Figure 7.1 shows the frequency of missing values across each of the variables collected for this chapter. Missingness varied from 0% to 56% (median 7%, IQR 2% to 32%). There are three dominant reasons for missing values. Firstly, for data entry into the GLOBALSTAR registry, the majority of the fields within this web-based database were not compulsory. A study researcher made

every effort to make the database as complete as possible, but since this was primarily an efficacy registry, some variables were not completed. Secondly, for several institutions research ethics approval did not allow access to patient identifiers. It was, therefore, impossible to contact specific sites with regard to missing database entries. Thirdly, there were several instances when preoperative CT scans could not be transferred to the study institution. Reasons for this included that the respective scan was not on PACS or that the local data transfer agreement prohibited transfer of any foreign CT scans. To clarify this last point, there were several instances where FEVAR was performed following a referral from another secondary care institution. The preoperative CT scan had been undertaken at the referring institution but the treating institution was not permitted to transfer imported CT data. Although it would have been advantageous, it was beyond time restrictions of this thesis to seek individual Trust approval for preoperative CT scans acquired outside of the nine participating institutions.

As previously stated data can be classified as missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR)(Rubin, 1976). For our data Little's MCAR test returned a test statistic of 5030 (P=0.11). There was not enough evidence to suggest that the missing data were not MCAR. Further missing value analyses were conducted where the cohort had been split on the basis of the proximal migration status (no or yes). The frequencies of present and missing values were compared between subgroups. Statistical testing was undertaken using Fisher's exact test, P values <0.05 were considered statistically significant. The following table provides an overview of the overall missing value analysis that have been presented in the appendix (Table 7.5).

Table 7.5 Summary of missing value tables presented in the appendices

Appendix	**Covariates**
APP_7	Baseline demographics and clinical
APP_8	Preoperative CT
APP_9	Graft design
APP_10	1st post-operative CT/database
APP_11	Follow-up changes CT/database

In some variables missing values were present in up to 56% of cases. Several variables had statistically significant differences in the number of missing values when comparing proximal migration status. These variables were those predominantly captured from the preoperative CT scan and the reasons for this have already been alluded to. Consideration of the effect of these missing values on the resultant assessment of predictive factors will be made in the discussion. A histogram summarising (Figure 7.1) the missing values together with a table (Table 7.6) describing those variables that have statistically significant differences in missing values are provided below.

Figure 7.1 An illustration of the frequencies of missing values across all covariates

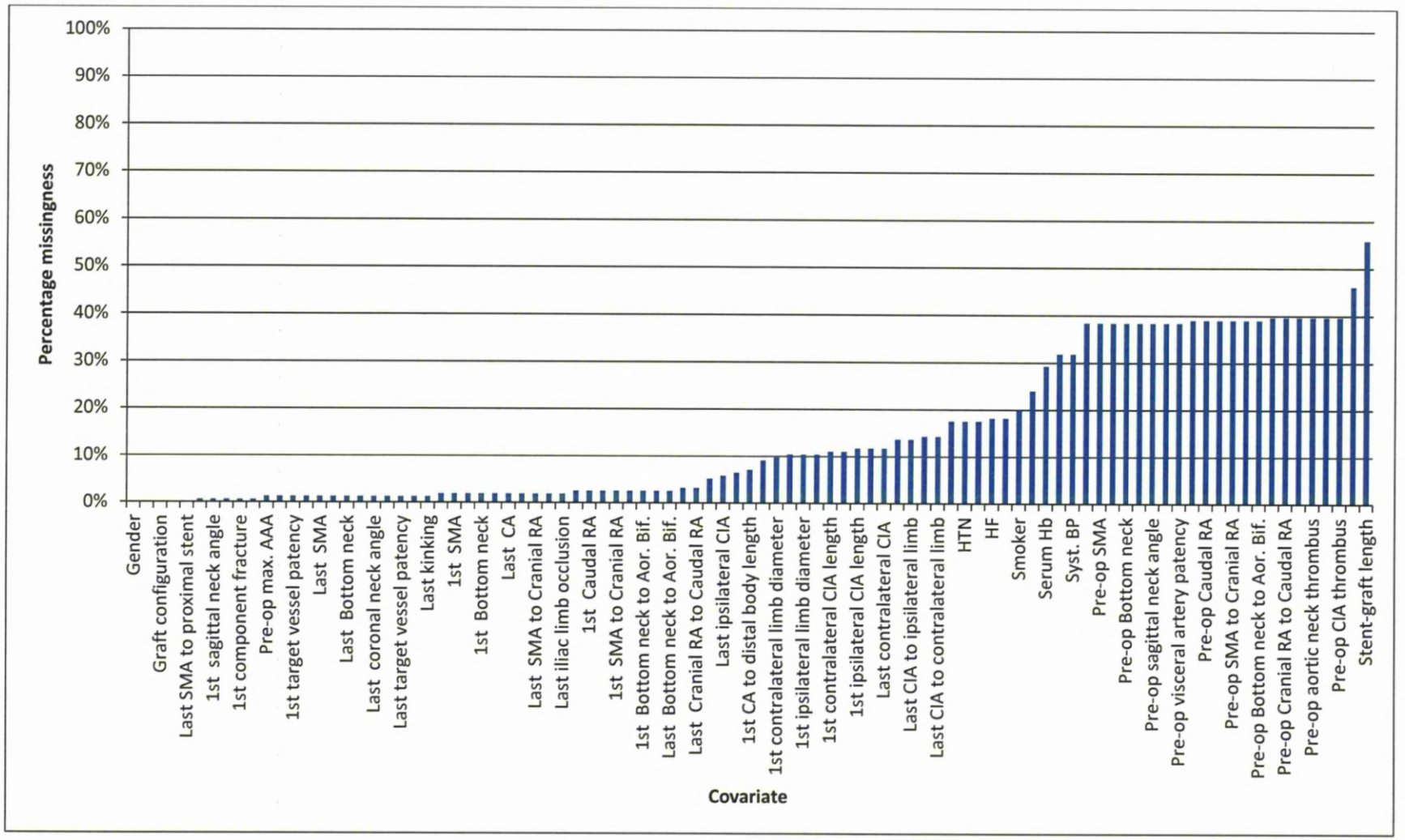


Table 7.6 Covariates with statistically significant differences in the numbers of missing values for proximal migration and non-migration groups.

	Covariate	Proximal migration: No (n=121) Present, n (%)	No (n=121) Missing, n (%)	Yes (n=33) Present, n (%)	Yes (n=33) Missing, n (%)	P Value
Diameters, mm	Coeliac axis (CA)	81 (67%)	40 (33%)	13 (39%)	20 (61%)	0.004
	Superior mesenteric artery (SMA)	82 (68%)	39 (32%)	13 (39%)	20 (61%)	0.003
	Cranial renal artery (CrRA)	82 (68%)	39 (32%)	13 (39%)	20 (61%)	0.003
	Caudal renal artery (CaRA)	81 (67%)	40 (33%)	13 (39%)	20 (61%)	0.004
	Bottom aortic neck (BN)	82 (68%)	39 (32%)	13 (39%)	20 (61%)	0.003
	Maximum common iliac artery (maxCIA)	81 (67%)	40 (33%)	13 (39%)	20 (61%)	0.004
Lengths, mm	CA to SMA	80 (66%)	41 (34%)	13 (39%)	20 (61%)	0.024
	SMA to CrRA	81 (67%)	40 (33%)	13 (39%)	20 (61%)	0.016
	CrRA to CaRA	80 (66%)	41 (34%)	13 (39%)	20 (61%)	0.021
	CaRA to BN	81 (67%)	40 (33%)	13 (39%)	20 (61%)	0.016
	CaRA to aortic bifurcation	81 (67%)	40 (33%)	13 (39%)	20 (61%)	0.016
	Common Iliac Artery (mean)	80 (66%)	41 (34%)	13 (39%)	20 (61%)	0.005
Angulation, °	Maximum coronal neck	82 (68%)	39 (32%)	13 (39%)	20 (61%)	0.003
	Maximum sagittal neck	82 (68%)	39 (32%)	13 (39%)	20 (61%)	0.003
Categorical	Aortic neck calcification	82 (68%)	39 (32%)	13 (39%)	20 (61%)	0.003
	Aortic neck thrombus	80 (66%)	41 (34%)	13 (39%)	20 (61%)	0.005
	Visceral artery patency	82 (68%)	39 (32%)	13 (39%)	20 (61%)	0.003
	CIA calcification	80 (66%)	41 (34%)	13 (39%)	20 (61%)	0.005
	CIA thrombus	80 (66%)	41 (34%)	13 (39%)	20 (61%)	0.005

P values were derived using Fisher's exact test. Diameters refer to aortic diameters unless otherwise specified.

7.3.3 Univariate (exploratory) analyses

The first phase of the formal analysis of risk factors was based exploratory univariate analyses. Initially, all available variables were included (continuous and categorical) and inferential statistical tests were conducted, when separating the groups according to proximal migration status. In order to assist with variable selection for the multivariate

analysis, any variable which produced a P value <0.1 was considered for possible inclusion. A further subgroup, who had P values <0.05, were subjected to a separate multivariate analysis. In view of the large dataset within this chapter, the summary statistics for each of the univariate analyses are provided within the appendices and their locations are detailed in the table below (*Table 7.7*).

Table 7.7 Tables outlining univariate analyses presented in the appendices

Appendix	Type of variables investigated
APP_12	Baseline demographic and clinical
APP_13	Preoperative CT morphology
APP_14	Graft-related
APP_15	Follow-up complications
APP_16	1st post-operative CT morphology
APP_17	Changes in morphology during follow-up

Those variables that have generated P values <0.1 are summarised in Table 7.9. With respect to clinical variables, heart rate, serum haemoglobin and smoking status were all identified as potential univariate risk factors for proximal migration. Review of the data showed that there were no clinical differences in heart rate between patients with and without evidence of proximal migration. Median (IQR) heart rate was 70 (64 to 82) beats per minute in the non-migration group whereas those with proximal migration the median (IQR) heart rate was 70 (57 to 74) beats per minute (P=0.07). Serum haemoglobin levels were higher in patients with proximal migration (median 14.4, IQR, 13.0 to 15.8 g/dL) compared to

the non-migration group (median 13.8, IQR, 13.0 to 14.8 g/dL; *P*=0.09). There were more past or current smokers in the proximal migration group (63/97, 65%) when compared with those without migration (21/26, 81%; *P*=0.09).

With regard to preoperative CT variables, proximal migration was more likely in patients with larger aortic necks. For patients with CT evidence of migration, median (IQR) aortic neck diameter was 24 (22 to 30) mm, whereas those patients without migration, the median (IQR) diameter was 23 (20 to 25) mm (*P*=0.07). Maximum coronal neck angle was lower in patients with proximal migration (median 17°, IQR 9° to 26°) when compared with those without migration (median 25°, IQR 13° to 38°; *P*=0.06). Moderate or severe CIA thrombus was more prevalent (22, 28%) in patients without proximal migration than those with (2, 15%; *P*=0.1).

There were three graft-related factors that were possible risk factors when subject to univariate analysis. Patients with two or more target vessel stents were greater in frequency, than the non-migration group (35/121, 29%) when compared patients to similar patients with proximal migration (5/33, 15%; *P*=0.08). Deployment of the ipsilateral limb in close proximity to the CIA bifurcation was found to be potentially protective of proximal migration. Patients with proximal migration had a median (IQR) ipsilateral limb deployment distance from the CIA of 20 (16 to 27) mm. This was greater than the median (IQR) length 15 (9-22) mm for the non-migration group (*P*=0.02). Larger diameter contralateral limbs were also suggested as being potentially protective of proximal migration. However, the clinical significance of this is questionable as the differences in limb diameters between the migration (median 13, IQR 11 to 13 mm) and non-migration groups (median 13, IQR 12 to 15 mm) were small (*P*=0.02).

Based on the 1st post-operative CT scan, proximal migration was greater in patients with larger aortic neck diameters (P=0.07), shorter aortic neck lengths (P=0.02), smaller contralateral CIA diameters (P=0.09) and smaller caudal renal artery to aortic bifurcation lengths (P=0.09). There were also some potential risk factors identifiable from changes in aortic morphology during follow-up. The incidence of proximal migration was greater in patients with expanding aortas, in these situations aortic diameters were measured at the coeliac axis (P=0.03), cranial (P=0.06) and caudal (P=0.03) renal arteries. Migration was also greater when the length of the SMA to cranial renal artery was shown to increase during follow-up (P=0.03) and when there was an increase in the inter-renal artery distance (P=0.08). Conversely, proximal migration appeared to be more prevalent in situations when the caudal renal artery to bifurcation length was decreasing (P=0.07). For follow-up complications, migration appeared to be more prevalent in cases where there was evidence of device kinking. By way of further clarification, in the non-migration group there was one case of stent-graft kinking (1/121, 1%) whereas there were three (3/33, 9%) in the proximal migration group (P=0.03). Further details on each of these factors are provided in Table 7.9 (P values <0.1) and Table 7.10 (P values <0.05). A tabulated summary of these results follows this paragraph (Table 7.8) and a further explanation with regarding these factors will form part of the discussion section.

Table 7.8 Summary of the covariates that achieved a statistically significant (P<0.05) association with proximal migration.

Covariate	No proximal migration (n=121)		Proximal migration (n=33)		P Value
	Median	IQR	Median	IQR	
Ipsilateral CIA deployment distance, mm	15.0	9 to 22	20.0	16 to 17	0.02
Contralateral limb diameter, mm	13.0	12 to 15	13.0	11 to 13	0.02
1st postop CT neck length, mm	5.0	0 to 11	0.0	0 to 7	0.02
Change in aortic diameter at CA, mm	1.0	0.0 to 2.0	2.0	0.5 to 4.0	0.03
Change in aortic diameter at CaRA, mm	2.0	1.0 to 4.0	4.0	2.0 to 7.0	0.03
Change in SMA to CrRA aortic length, mm	1.0	-2.0 to 2.0	2.0	-0.8 to 4.0	0.03
Graft kinking	1 (1%)		3 (9%)		0.03

IQR, inter-quartile range. CA, coeliac axis. CaRA, caudal renal artery. CrRA, cranial renal artery.

Table 7.9 Univariate analysis, variables which showed an association with proximal migration (≥ 4 mm) by a P value (<0.1)

		No Proximal Migration (n=121)							Proximal Migration (n=33)							P value
		n (%)	Normality test P value	Mean	SD	Median	IQR	Min, Max	n (%)	Normality test P value	Mean	SD	Median	IQR	Min, Max	
CLINICAL	Heart rate (b.p.m)		<0.01	72	13	70	64 - 82	49, 100		0.02	68	16	70	57 - 74	48, 112	0.07
	Serum haemoglobin (g/dl)		<0.01	13.7	1.6	13.8	13.0 - 14.8	9.5, 16.6		0.17	14.3	1.6	14.4	13.3 - 15.8	11, 16.5	0.09
	Ex-/current smoker	63 (65%)							21 (81%)							0.09
GRAFT	≥ 2 TV stented	35 (29%)							5 (15%)							0.08
	Ipsilateral CIA deploy. dist.		<0.01	16	12	15	9 - 22	-47, 54		0.75	20	9	20	16 - 27	-1, 36	0.02
	Contralateral limb diameter		<0.01	14	3	13	12 - 15	8, 28		<0.01	13	3	13	11 - 13	7, 20	0.02
PRE-OP CT	Pre-op bottom neck diameter		<0.01	23	4	23	20 - 26	16, 35		0.13	25	5	24	22 - 30	18, 37	0.07
	Max. coronal neck angulation		<0.01	27	18	25	13 - 38	0, 70		0.45	17	9	17	9 - 26	2, 30	0.06
	Maximum CIA thrombus	33 (28%)							5 (15%)							0.10
1ST POST-OP CT	1st bottom neck diameter		<0.01	23	4	23	20 - 26	16, 35		0.13	25	5	24	22 - 30	18, 37	0.07
	1st contralateral CIA diameter		<0.01	13	3	13	11 - 15	8, 22		0.04	12	3	12	11 - 14	8, 20	0.09
	1st aortic neck length		<0.01	6	7	5	0 - 11	0, 25		<0.01	3	5	0	0 - 7	0, 17	0.02
	1st CaRA to Aortic Bif length		<0.01	123	19	120	110 - 134	86, 190		<0.01	129	18	124	117 - 136	108, 184	0.09
FOLLOW-UP CT CHANGES	Coeliac axis (CA) diameter		<0.01	1.2	2.3	1.0	0.0 - 2.0	-3.0, 14.0		0.57	2.0	2.6	2.0	0.5 - 4.0	-4.0, 9.0	0.03
	Cranial RA diameter (CrRA)		<0.01	2.5	2.4	2.0	1.0 - 4.0	-2.0, 12.0		0.88	3.6	3.2	4.0	1.0 - 6.0	-3.0, 11.0	0.06
	Caudal RA diameter (CaRA)		<0.01	2.9	2.4	2.0	1.0 - 4.0	-1.0, 12.0		0.35	4.1	3.1	4.0	2.0 - 7.0	-1.0, 11.0	0.03
	SMA to CrRA length		<0.01	0.1	4.8	1.0	-2.0 - 2.0	-22.0, 18.0		<0.01	2.4	5.0	2.0	-0.8 - 4.0	-7.0, 17.0	0.03
	CrRA to CaRA length		<0.01	0.1	3.9	0.0	-2.0 - 2.0	-16.0, 11.0		<0.01	1.0	3.5	1.0	0.0 - 2.8	-10.0, 6.0	0.08
	CaRA to Aortic Bif. length		<0.01	-2.1	8.9	-2.0	-8.0 - 1.8	-28.0, 30.0		0.01	-7.1	14.7	-6.0	-13.0 - 1.0	-53.0, 30.0	0.07
	Graft kinking	1 (1%)							3 (9%)							0.03

Normality was assessed using the Shapiro-Wilk test. SD, standard deviation; IQR, inter-quartile range; Min, minimum; Max, maximum. P values for categorical variables (indicated by an asterisk*) are expressed using the Fisher Exact test. Parameters shaded in grey refer to the appropriate descriptive statistic when considering the distribution of the data. Vessel quality indices e.g. aortic neck calcification were subdivided into none or mild versus moderate or severe. Follow-up changes are with respect to the aorta.

Table 7.10 Univariate analysis, variables which showed an association with proximal migration (≥ 4 mm) by a P value (<0.05)

		No Proximal Migration (n=131)							Proximal Migration (n=33)							P value
		n (%)	Normality test P value	Mean	SD	Median	IQR	Min, Max	n (%)	Normality test P value	Mean	SD	Median	IQR	Min, Max	
GRAFT	Ipsilateral CIA deploy. dist.		<0.01	16	12	15	9 - 22	-47, 54		0.75	20	9	20	16 - 27	-1, 36	0.02
	Contralateral limb diameter		<0.01	14	3	13	12 - 15	8, 28		<0.01	13	3	13	11 - 13	7, 20	0.02
1ST POST-OP CT	1st aortic neck length		<0.01	6	7	5	0 - 11	0, 25		<0.01	3	5	0	0 - 7	0, 17	0.02
FOLLOW-UP CT CHANGES	Coeliac axis (CA) diameter		<0.01	1.2	2.3	1.0	0.0 - 2.0	-3.0, 14.0		0.57	2.0	2.6	2.0	0.5 - 4.0	-4.0, 9.0	0.03
	Caudal RA diameter (CaRA)		<0.01	2.9	2.4	2.0	1.0 - 4.0	-1.0, 12.0		0.35	4.1	3.1	4.0	2.0 - 7.0	-1.0, 11.0	0.03
	SMA to CrRA length		<0.01	0.1	4.8	1.0	-2.0 - 2.0	-22.0, 18.0		<0.01	2.4	5.0	2.0	-0.8 - 4.0	-7.0, 17.0	0.03
	Graft kinking	1 (1%)							3 (9%)							0.03

Normality was assessed using the Shapiro-Wilk test. SD, standard deviation; IQR, inter-quartile range; Min, minimum; Max, maximum. P values for categorical variables (indicated by an asterisk*) are expressed using the Fisher Exact test. Parameters shaded in grey refer to the appropriate descriptive statistic when considering the distribution of the data. Vessel quality indices e.g. aortic neck calcification were subdivided into none or mild versus moderate or severe.

7.3.4 Multivariate analyses

Univariate analyses have identified several risk factors that were associated with proximal migration of a Zenith fenestrated stent-graft (Table 7.8). The focus for this thesis now turns to the evaluation of multiple factors within a single statistical model. Ideally, results from the model will allow the prediction of proximal migration of a fenestrated stent-graft from one or more independent variables. Proximal migration is measured in a continuous scale, but from previous validation experiments, there is uncertainty regarding the accuracy of any migration measurements that are less than four millimetres. Due to this limitation migration is considered as a binary event (movement ≥ 4 mm) and modelled as a categorical (binary) variable. Various methods exist for investigating the effect of multiple variables on an event. The event migration is not the only concern within this project but also the time to the event. In order to use the time data within the model, a multiple regression analysis using a Cox proportion hazards model has been constructed. The Cox model has several available options in order to consider multiple variables and can also model the time to event when the data is interval censored. Modelling using interval censored data has previously proven to be difficult and the majority of commercially available computer programmes require a precise event time (i.e. SPSS Statistics for Windows).

The first stage in the multivariate analysis will utilise the statistical software package R. This package provides the option of a Cox regression analysis using pre-specified event times (beginning of the interval, midpoint and end of the interval) together with the option of an interval censoring approach. In order to construct a Cox model using interval censored

data the R package requires the add-on package 'Intcox' (Wei, 1999). Although the original paper by Wei was published in 1999, the integration of this function (Cox proportional hazards model using interval censored data) has only been available in R from February 2013. The output from this package provides a hazard ratio (exponential regression coefficient) but no indication of 95% confidence intervals or resultant P values. 95% confidence intervals can be generated using the Intcox package and a separate bootstrapping technique.

In statistics, bootstrapping is a method of assigning measures of accuracy to sample estimates (Efron and Tibshirani, 1993). This computer sampling technique allows the generation of an estimate of the sampling distribution of almost any statistic using very simple methods (Varian, 2005). The theory behind bootstrapping is to repeatedly sample (with replacement) from a single sample. Using these new "samples" to compute the sampling distribution for the statistics related to the problem. With respect to regression, bootstrapping can be used to generate related confidence intervals (Campbell and Torgerson, 1999). Simply, the Intcox function was run repeatedly with removal of a single case each time in order to generate a series of regression coefficients. The bootstrapping method was asked to generate 100 regression coefficients for the same variable and then rank them in order. Values in positions 3 and 97 provide approximate 95% confidence intervals. This procedure was completed for all hazard ratio calculations that used interval censored data. If the confidence interval did not cross 1 then the hazard ratio was considered to be statistical significant i.e $P<0.05$. R codes for the calculation of survival data, Cox proportional hazards models and bootstrapping techniques are provided within the appendices.

Within the statistical programming language R, there are limited options for how selected variables are entered within the Cox model. The default option is the 'enter' method where all selected variables are entered at the same time. SPSS Statistics for Windows 20.0 has a greater range of options, in addition to the enter method there is the further option of step-wise regression. Step-wise regression allows the software to determine the order of entry of a variable. There are two stepwise options, forward and backward, a forward method is where the variable that causes the greatest increase R^2 is selected first. There is also the option of starting with a full model of all selected variables and then eliminating variables that do not significantly enter the regression equation and a partial model is found. This is described as a *backward* variable entry procedure. Both forward and backward regression options are readily available using SPSS, however, a forward and backward model cannot be generated in SPSS using interval censored data. The impact of this will be considered within the discussion section.

When using covariates which generated a univariate P value (<0.1), there were no statistically significant variables identified using a multivariate Cox proportional hazards model. These findings were consistent across the two statistical packages and for all event time definitions. This absence of any statistically significant variables was also seen for the different variable entry methods (Enter, Forward and Backward). A series of tables providing summary statistics are presented in the appendices, the locations of which are described in the table below (Table 7.11).

Table 7.11 Description of the Cox proportional hazards models that are resented in the appendices

Appendix	Cox Proportional Hazards Model
APP_18	R, beginning of interval (P<0.1)
APP_19	R, midpoint of interval (P<0.1)
APP_20	R, end of interval (P<0.1)
APP_21	SPSS, beginning of interval (P<0.1)
APP_22	SPSS, midpoint of interval (P<0.1)
APP_23	SPSS, end of interval (P<0.1)

With regard to those variables that produce a *P* Value <0.05. Results from this multivariate analysis are first described using the R programme (Table 7.12). Results using the computer programme SPSS Statistics for Windows 20.0 are summarised in Table 7.13, these included results from the forward and backward stepwise regression models.

Table 7.12 Multivariate analysis of risk factors for proximal migration using R and the four event time definitions

Event time definition	Univariate				Multivariate			
		95%CI				95%CI		
Beginning of interval	HR	Lower	Upper	P Value	HR	Lower	Upper	P Value
Ipsilateral CIA deployment distance, mm	1.02	0.99	1.05	0.17	1.02	0.98	1.06	0.26
Contralateral limb diameter, mm	0.85	0.75	0.97	0.02	0.88	0.74	1.05	0.16
1st aortic neck length, mm	0.91	0.84	0.97	0.01	0.91	0.84	0.99	0.02
Diameter change - coeliac axis, mm	1.08	0.97	1.20	0.18	1.03	0.89	1.19	0.71
Diameter change - caudal renal artery, mm	1.11	0.98	1.25	0.09	1.22	1.03	1.44	0.02
Length change, SMA to caudal renal artery, mm	1.07	1.01	1.14	0.03	1.16	1.04	1.28	0.01
Graft kinking	1.70	0.65	4.42	0.28	0.42	0.05	3.21	0.40
Midpoint of interval								
Ipsilateral CIA deployment distance, mm	1.02	0.99	1.05	0.29	1.02	0.99	1.06	0.25
Contralateral limb diameter, mm	0.85	0.75	0.97	0.02	0.86	0.72	1.04	0.12
1st aortic neck length, mm	0.90	0.83	0.97	0.00	0.90	0.83	0.97	0.01
Diameter change - coeliac axis, mm	1.08	0.97	1.21	0.14	1.02	0.88	1.19	0.75
Diameter change - caudal renal artery, mm	1.10	0.97	1.24	0.15	1.18	1.00	1.39	0.06
Length change, SMA to caudal renal artery, mm	1.06	1.00	1.13	0.07	1.12	1.01	1.24	0.02
Graft kinking	1.84	0.71	4.79	0.21	0.52	0.07	3.98	0.53
Endpoint of interval								
Ipsilateral CIA deployment distance, mm	1.01	0.98	1.04	0.48	1.02	0.98	1.05	0.38
Contralateral limb diameter, mm	0.84	0.73	0.95	0.01	0.84	0.70	1.02	0.09
1st aortic neck length, mm	0.89	0.83	0.96	0.00	0.90	0.83	0.97	0.01
Diameter change - coeliac axis, mm	1.08	0.97	1.20	0.17	1.01	0.87	1.18	0.87
Diameter change - caudal renal artery, mm	1.07	0.94	1.22	0.29	1.12	0.95	1.33	0.18
Length change, SMA to caudal renal artery, mm	1.05	0.98	1.12	0.14	1.10	0.99	1.21	0.07
Graft kinking	1.79	0.69	4.65	0.23	0.61	0.08	4.78	0.64
Interval censoring								
Ipsilateral CIA deployment distance, mm	1.01	0.98	1.05	>0.05	1.02	0.97	1.06	>0.05
Contralateral limb diameter, mm	0.85	0.72	0.94	<0.05	0.84	0.57	0.95	<0.05
Aortic neck length, mm	0.91	0.86	0.97	<0.05	0.90	0.78	0.97	<0.05
Diameter change - coeliac axis, mm	1.07	0.97	1.25	>0.05	1.01	0.81	1.21	>0.05
Diameter change - caudal renal artery, mm	1.10	0.97	1.24	>0.05	1.12	0.91	1.48	>0.05
Length change, SMA to caudal renal artery, mm	1.09	1.02	1.16	<0.05	1.10	0.96	1.28	>0.05
Graft kinking	0.53	0.00	1.78	>0.05	0.61	0.00	3.40	>0.05

Variables were selected from univariate analysis (P<0.05) and entry into the R package used the ENTRY method. Values in red indicate those variables that were statistically significant (P<0.05) when using multivariate analysis. Univariate HR were provided for additional information.

Table 7.13 Multivariate analysis of risk factors for proximal migration using SPSS (covariates returning P<0.05 on univariate analysis).

VARIABLE SELECTION METHOD	ENTER				FORWARD				BACKWARD			
Event time definition	HR	95.0% CI for HR		P Value	HR	95.0% CI for HR		P Value	HR	95.0% CI for HR		P Value
		Lower	Upper			Lower	Upper			Lower	Upper	
Beginning of interval												
Ipsilateral CIA deployment distance, mm	1.02	0.99	1.06	0.25								
Contralateral limb diameter, mm	0.88	0.74	1.05	0.17					0.88	0.75	1.04	0.13
Aortic neck length, mm	0.91	0.84	0.99	0.02	0.92	0.85	0.99	0.03	0.92	0.85	0.99	0.03
Diameter change - coeliac axis, mm	1.04	0.89	1.20	0.63								
Diameter change - caudal renal artery, mm	1.20	1.02	1.41	0.03	1.22	1.05	1.42	0.01	1.21	1.04	1.41	0.01
Length change, SMA to caudal renal artery, mm	1.14	1.03	1.26	0.01	1.15	1.05	1.27	0.01	1.14	1.04	1.25	0.01
Graft kinking	2.24	0.29	16.98	0.44								
Midpoint of interval												
Ipsilateral CIA deployment distance, mm	1.02	0.99	1.06	0.24								
Contralateral limb diameter, mm	0.86	0.72	1.04	0.12					0.87	0.73	1.03	0.10
Aortic neck length, mm	0.90	0.83	0.97	0.01	0.91	0.84	0.98	0.01	0.91	0.84	0.98	0.01
Diameter change - coeliac axis, mm	1.02	0.88	1.19	0.76								
Diameter change - caudal renal artery, mm	1.18	0.99	1.39	0.06	1.19	1.02	1.38	0.02	1.18	1.02	1.38	0.03
Length change, SMA to caudal renal artery, mm	1.12	1.01	1.24	0.02	1.14	1.04	1.25	0.01	1.18	1.02	1.38	0.01
Graft kinking	1.94	0.25	14.94	0.53								
Endpoint of interval												
Ipsilateral CIA deployment distance, mm	1.02	0.98	1.05	0.38								
Contralateral limb diameter, mm	0.84	0.70	1.02	0.08	0.83	0.70	0.98	0.03	0.84	0.70	1.00	0.05
Aortic neck length, mm	0.90	0.83	0.97	0.01	0.91	0.84	0.98	0.01	0.91	0.84	0.98	0.01
Diameter change - coeliac axis, mm	1.01	0.87	1.18	0.87								
Diameter change - caudal renal artery, mm	1.12	0.95	1.33	0.18								
Length change, SMA to caudal renal artery, mm	1.10	0.99	1.21	0.07					1.09	0.99	1.20	0.07
Graft kinking	1.63	0.21	12.72	0.64								

Variables were selected from univariate analysis (P<0.05) and entry into the SPSS package. Values in red indicate those variables that were statistically significant (P<0.05) when using multivariate analysis.

Multivariate analysis based on the Cox proportional hazard model using the R statistical package (interval censoring) revealed that 1st postoperative aortic neck length measurement is a risk factor for proximal migration (HR 0.9, 95%CI 0.78 to 0.97, P<0.05). This covariate was statistically significant across all three other event time definitions and the effect occurred in a negative direction. For every unit increase (mm) in 1st postoperative neck length there is a 9-10% decrease in the proximal migration hazard. Taking into consideration the 95% confidence intervals this decrease in hazard can vary between 1% and 22%.

When using the beginning of the interval as the event time definition, follow-up changes in aortic diameter at the most caudal renal artery (HR 1.22, 95%CI 1.03 to 1.44, *P*=0.02) and changes in the SMA to cranial renal artery distance were also found to be risk factors (HR 1.16, 95%CI 1.04 to 1.28, *P*=0.01). For every mm increase in aortic diameter at the most caudal renal artery during follow-up there was a 22% (95%CI 3% – 44%) increase in proximal migration hazard. For changes in the SMA to the cranial renal artery length, every mm increase during follow-up will cause an estimated 16% (95%CI 4% – 28%) rise in proximal migration hazard. This last covariate was also found to be statistically significant when using the midpoint of the interval as the event time (HR 1.12, 95% CI 1.01 to 1.24, *P*=0.02). Using an interval censoring event time definition, contralateral iliac limb diameter was found to have a negative effect on the risk of proximal migration (HR 0.84, 95%CI 0.57 to 0.95, P<0.05). For every unit increase (mm) in contralateral limb diameter, there was an estimated 16% (95% 5% to 43%) reduction in the proximal migration hazard.

There were many similarities when using the SPSS 'enter' method. For all three specific event time definitions the 1st postoperative aortic neck length was found to be a risk

factor for proximal migration. Hazard rates were similar showing around a 10% reduction for every additional mm in aortic neck length. When using the beginning of interval event time definition there were further consistencies. Follow-up aortic diameter changes at the caudal renal artery and an increase in SMA to cranial renal artery length were also found to be risk factors, with similar hazard ratios. Follow-up aortic diameter changes at the most caudal renal artery escaped statistical significant (P=0.06) when using the midpoint event time definition. However, postoperative changes in the SMA to cranial renal artery length were associated with proximal migration, when using this event time (HR 1.12, 95%CI 1.01 to 1.24, P=0.02). When using the end of the interval, the 1st postoperative aortic neck length was the only statistically significant variable, producing similar hazard ratios to the R package (HR 0.9, 95%CI 0.83 to 0.97, P=0.01).

When using the SPSS stepwise forward and backward variable entry methods, the following results were observed. Using forward selection, 1st postoperative CT aortic neck length, postoperative aortic diameter changes at the most caudal renal artery and length changes between the SMA and caudal renal artery were found to be statistically significant. This was only when using the beginning and midpoints of the interval as event times. When using the endpoint of the interval, follow-up length changes were not included in the model and the contralateral limb diameter was included (HR 0.83, 95%CI 0.70 to 0.98, P=0.03). Using a backward selection process produced almost identical results to forward selection for the beginning and midpoints of the interval (event times). When using the end of the interval, the 1st postoperative CT aortic neck length measurement was the only statistically significant risk factor (HR 0.91, 95% CI 0.84 to 0.98, P=0.01). A summary of possible changes to covariates and their resultant effects on the migration hazards are described in Table 7.14.

Table 7.14 Effect of possible variable changes on the proximal migration hazards.

Variable	Model	Event time definition	Migration Hazard (1 unit rise)
Postoprative 1st CT aortic neck length, mm	R (Enter)	Beginning	9% decrease
		Midpoint	10% decrease
		Endpoint	10% decrease
		Interval censoring	10% decrease
	SPSS (Enter)	Beginning	9% decrease
		Midpoint	10% decrease
		Endpoint	10% decrease
	SPSS (Forward)	Beginning	8% decrease
		Midpoint	9% decrease
		Endpoint	9% decrease
	SPSS (Backward)	Beginning	8% decrease
		Midpoint	9% decrease
		Endpoint	9% decrease
Aortic diameter changes at most caudal renal artery, mm	R (Enter)	Beginning	22% increase
		Midpoint	12% increase
	SPSS (Enter)	Beginning	20% increase
		Midpoint	18% increase
	SPSS (Forward)	Beginning	22% increase
		Midpoint	19% increase
	SPSS (Backward)	Beginning	21% increase
		Midpoint	18% increase
Length changes from SMA to cranial renal artery, mm	R (Enter)	Beginning	16% increase
		Midpoint	12% increase
	SPSS (Enter)	Beginning	14% increase
		Midpoint	12% increase
Contralateral limb diameter, mm	R (Enter) SPSS (Forward)	Interval censoring	16% decrease
		Endpoint	17% decrease

7.3.5 Multiple imputations (MI) and missing data recovery

Missing data are a common problem in all types of medical research. As Donders and colleagues reported there are various methods available to handle missing data (Donders *et al.*, 2006). Simple and commonly used methods include complete or available case analysis, the missing-indicator method (Miettinen, 1985), hot deck imputation (Andridge and Little, 2010) and overall mean imputation (Shrive *et al.*, 2006). Reports have argued that these methods can lead to an inefficient analysis and more seriously can produce severely biased estimates of any associations (Greenland and Finkle, 1995, Vach, 1994, Rubin, 1987, Schafer, 1997, Little, 1992). With improvements in statistical programming and computer technology, there are now more sophisticated imputation techniques to handle missing data. One of these techniques replaces missing values for any given subject based on a computer prediction from known characteristics. This technique is termed multiple imputations (MI). MI is a Monte Carlo technique in which missing values are replaced by $m>1$ simulated versions, where m is typically small (e.g. 3-10). Commonly available statistical programmes provide the option for MI (e.g. SAS, R and SPSS).

One of the limitations of the multicentre cohort was the presence of missing values for some variables. The accuracy of the Cox proportional hazards model may be improved by modelling for missing values using a technique such as MI. The computer programme IBM SPSS Statistics for Windows 20.0 (IBM Corp, Armonk, NY) provides an option for MI. Within this thesis, the original multicentre dataset (with missing values, see previous section) was subject to an MI procedure. This resulted in the generation of 5 additional MI datasets (MI-1, MI-2, MI-3, MI-4 and MI-5) with no missing values. Descriptive statistics for the seven

covariates tested within the original $P<0.05$ Cox proportional hazards model and the new MI datasets are summarised below (Table 7.14).

Table 7.15 Summary statistics for original and alternative (multiple imputation) datasets (MI-1 to MI-5)

Variable	Dataset	Missingness n (%)	Normality test, P value	Mean	SD	Median	IQR	Min, Max
1st postoperative CT neck length, mm	Original	4 (3%)	<0.001	5.6	6.3	4.0	0.0 to 10.0	0.0, 25.0
	MI-1	0 (0%)	<0.001	5.6	6.3	4.0	0.0 to 10.0	0.0, 25.0
	MI-2	0 (0%)	<0.001	5.5	6.3	4.0	0.0 to 10.0	0.0, 25.0
	MI-3	0 (0%)	<0.001	5.7	6.3	4.0	0.0 to 10.0	0.0, 25.0
	MI-4	0(%)	<0.001	5.6	6.3	4.0	0.0 to 10.0	0.0, 25.0
	MI-5	0 (0%)	<0.001	5.7	6.3	4.0	0.0 to 10.0	0.0, 25.0
Follow-up aortic neck diameter change – coeliac axis, mm	Original	5 (3%)	<0.001	1.4	2.4	1.0	0.0 to 2.0	-3.0, 14.0
	MI-1	0 (0%)	<0.001	1.4	3.4	1.0	0.0 to 2.0	-4.0, 14.0
	MI-2	0 (0%)	<0.001	1.3	2.4	1.0	0.0 to 2.0	-4.0, 14.0
	MI-3	0 (0%)	<0.001	1.4	2.4	1.0	0.0 to 2.0	-4.0, 14.0
	MI-4	0 (0%)	<0.001	1.4	2.4	1.0	0.0 to 2.0	-4.0, 14.0
	MI-5	0 (0%)	<0.001	1.4	2.4	1.0	0.0 to 2.0	-4.0, 14.0
Follow-up aortic neck diameter change - caudal renal artery, mm	Original	6 (4%)	<0.001	3.3	2.4	3.0	2.0 to 5.0	-1.0, 10.0
	MI-1	0 (0%)	<0.001	3.2	2.6	3.0	1.0 to 5.0	-1.0, 12.0
	MI-2	0 (0%)	<0.001	3.2	2.6	3.0	1.0 to 5.0	-1.0, 12.0
	MI-3	0 (0%)	<0.001	3.2	2.6	3.0	1.0 to 5.0	-1.0, 12.0
	MI-4	0 (0%)	<0.001	3.2	2.6	3.0	1.0 to 5.0	-1.0, 12.0
	MI-5	0 (0%)	<0.001	3.2	2.6	3.0	1.0 to 5.0	-1.0, 12.0
Contralateral limb diameter, mm	Original	15 (10%)	<0.001	13.7	3.2	13.0	12.0 to 15.0	8.0, 28.0
	MI-1	0 (0%)	<0.001	13.6	3.2	13.0	11.8 to 15.0	7.0, 28.0
	MI-2	0 (0%)	<0.001	13.6	3.1	13.0	12.0 to 15.0	7.0, 28.0
	MI-3	0 (0%)	<0.001	13.6	3.2	13.0	11.8 to 15.0	7.0, 28.0
	MI-4	0 (0%)	<0.001	13.6	3.2	13.0	11.9 to 15.0	7.0, 28.0
	MI-5	0 (0%)	<0.001	13.6	3.2	13.0	12.0 to 15.0	7.0, 28.0
Ipsilateral limb deployment distance, mm	Original	27 (18%)	<0.001	17.0	12.2	16.6	9.8 to 23.9	-46.8, 53.6
	MI-1	0 (0%)	<0.001	16.7	10.8	16.5	10.3 to 21.8	-46.8, 53.6
	MI-2	0 (0%)	<0.001	16.7	10.8	16.3	10.3 to 21.8	-46.8, 53.6
	MI-3	0 (0%)	<0.001	16.7	10.9	16.5	10.1 to 21.9	-46.8, 53.6
	MI-4	0 (0%)	<0.001	16.8	10.9	16.3	10.6 to 21.8	-46.8, 53.6
	MI-5	0 (0%)	<0.001	16.6	10.8	16.0	10.6 to 21.1	-46.8, 53.6
Follow-up change SMA to cranial renal artery length, mm	Original	5 (3%)	<0.001	-0.7	3.9	-1.0	-2.0 to 1.8	17.0, 11.0
	MI-1	0 (0%)	<0.001	-0.6	5.0	-1.0	-3.0 to 2.0	-18.0, 22.0
	MI-2	0 (0%)	<0.001	-0.6	4.9	-1.0	-3.0 to 2.0	18.0, 22.0
	MI-3	0 (0%)	<0.001	-0.6	5.0	-1.0	-3.0 to 2.0	-18.0, 22.0
	MI-4	0 (0%)	<0.001	-0.6	5.0	-1.0	-3.0 to 2.0	18.0, 22.0
	MI-5	0 (0%)	<0.001	-0.5	5.0	-1.0	-3.0 to 2.0	-18.0, 22.0

SD, standard deviation. IQR, inter-quartile range. MI- missing imputation dataset. Min, minimum. Max, maximum. Base on the distribution of the data the shaded area highlights the appropriate descriptive statistics.

The multiple imputation technique recovered a total of 63 missing values across the seven variables. Comparison of the datasets generated using the MI process (MI1 to MI5) demonstrated very little difference in the summary statistics (Table 7.15). The Cox proportional hazards model was then reapplied to each of the five alternative datasets (MI-1

to MI-5). The original seven included covariates remained the same as did the four event time definitions. Generating the Cox proportional hazards model using five additional MI datasets produced a significant amount of data. These have been summarised within the appendices, the full detail on the locations of these results are provided in the table below (Table 7.16).

Table 7.16 *Location of Cox proportional hazards models for the MI datasets within the appendices.*

Appendix	Cox Proportional Hazards Models for MI datasets
APP_24	1st postoperative CT aortic neck length
APP_25	Postop aortic diameter change – coeliac axis
APP_26	Postop aortic diameter change – caudal renal artery
APP_27	Contralateral limb diameter
APP_28	Ipsilateral iliac limb deployment distance
APP_29	Graft kinking
APP_30	Postop change in length, SMA to cranial renal artery

For the 1st postoperative CT aortic length measurement, this was identified as a statistically significant risk factor across all MI datasets, for all event time definitions and with all modelling techniques. There was additional consistently, a 10% hazard reduction from every unit increase in 1st postoperative CT aortic neck length was similar to the Cox HR estimates using the original dataset. 95% CI were also consistent across all event time definitions and between datasets.

Follow-up changes in aortic diameter, at the level of the coeliac axis, were not found to be a statistically significant risk factor for proximal migration with any of the MI datasets. This feature was consistent with the original dataset and was not affected by event time definition or modelling process e.g. SPSS or R. Follow-up changes in aortic diameter at the level of the most caudal renal artery did, however, provide some further evidence that this may be a risk factor. Using the original data this variable was found to be significant when using the beginning and midpoint of the interval. Introduction of the MI datasets produced similar results and also identified this as a risk factor when using the end of the interval (forward and backward stepwise selection on SPSS, 2 out of 5 MI datasets only). When using the original dataset the contralateral iliac limb diameter was found to be a risk factor, when using R and an interval censoring approach. For each of the five new MI datasets, statistically significant differences, for all event times and using all approaches, were demonstrated for the contralateral limb diameter. Originally, the contralateral limb diameter was missing in 10% of patients, compensating using an MI technique is a possible reason for the more widespread statistical significance. For the MI datasets hazard ratios ranged from 0.79 (95% CI 0.67 to 0.93, P=0.01) to 0.87 (95% CI 0.77 to 0.99, P=0.04).

Ipsilateral iliac limb deployment distance was not found to be a risk factor on multivariate analysis (HR 1.02, 95%CI 0.98 to 1.06; P=0.26). This was a consistent feature across all five of the MI datasets and a similar trend can be reported for graft kinking (HR 0.42, 95%CI 0.1 to 3.2; P=0.4). Postoperative changes to the SMA to cranial renal artery distance were shown to be a risk factor when using the original dataset for the beginning and midpoint of the interval event times. This observation included both the R and SPSS statistical programmes and forward and backward stepwise entry approaches (SPSS only).

These findings were consistent across the MI datasets, however, there were several situations where this variable was also found to be statistically significant (e.g. endpoint of the interval). There was, however, an opposite trend for this variable, in that the direction of effect was negative for the MI datasets and positive with the original data. This raises questions on the reliability of the MI processes in this instance and further commentary on the MI process will form part of the discussion.

Stepwise regression is a semi-automated process for building a model by successively adding or removing variables. Depending on the dataset there could be differences in the resultant models. The 1st post-operative neck length measurement was included in all stepwise models. When using the original dataset, the second and third commonest variables to be included were postoperative changes in aortic diameter (caudal renal artery) and changes in the SMA to cranial renal artery length. These were both selected when using the beginning of the interval and midpoint and for both forward and backward selection processes. Contralateral limb diameter was included in the original data model when using interval censoring, together with 1st postoperative aortic neck length (not a stepwise approach). This was at the expense of any changes in aortic morphology during follow-up. The addition of the MI datasets included the contralateral limb diameter for all situations all of the MI datasets. Changes in aortic diameter were included in 2 out of 5 MI datasets for both the beginning and midpoints of the interval (forward stepwise). In general, there was consistency between the forward and backward stepwise selection processes. There were some slight differences between MI datasets and event time definitions used. Full details on the comparison between datasets are provided in Table 7.17 and Table 7.18.

Table 7.17 Comparison between the original and MI datasets with regard to variables selected in a forward SPSS stepwise model.

Dataset/Variable	Original	MI-1	MI-2	MI-3	MI-4	MI-5
1st postoperative neck length, mm	B M E	B M E	B M E	B M E	B M E	B M E
Aortic diameter change – caudal renal artery, mm	B M	B M	B M	B	M	B M
Contralateral iliac limb diameter, mm	E	B M E	B M E	B E	B M E	B M E
Post-operative length change – SMA to cranial renal artery, mm	B M	B	B	B	M	B

Event time - B, beginning of interval; M, middle of interval; E, end of interval. All variables identified in the first column generated P values <0.05 using Cox regression.

Table 7.18 Comparison between the original and MI datasets with regard to variables selected in a backward SPSS stepwise model.

Dataset/variable	Original	MI-1	MI-2	MI-3	MI-4	MI-5
1st postoperative aortic neck length, mm	B M E	B M E	B M E	B M E	B M E	B M E
Aortic diameter change – caudal renal artery, mm	B M	B M	B M	B M E	B M	B M
Contralateral iliac limb diameter, mm	E	B M E	B M E	B M E	B M E	B M E
Post-operative length change – SMA to cranial renal artery, mm	B M	B M	B M	B M	B M	B

Event time - B, beginning of interval; M, middle of interval; E, end of interval. All variables identified in the first column generated P values <0.05 using Cox regression.

7.4 Discussion

Fenestrated stent-grafts are expensive, aneurysm morphology is complex and migration-related complications are potentially catastrophic. For manufacturers, clinicians and patients the identification of risk factors for proximal migration is likely to bring benefit. Using data from the previous chapter, it is estimated that a third of patients will experience proximal migration by 4 years. With this incidence, it is appropriate to consider causative factors and whether migration can be predicted in the future. To date, this is the first in man study to

quantify fenestrated stent-graft migration using a previously validated technique (Chapter 4). Several clinical, anatomical, graft-related and follow-up variables have been previously linked with the migration of a conventional (infrarenal) stent-graft. For fenestrated stent-grafts, no such reports exist, any speculation regarding risks factors are based on a small number of lab experiments, comparisons with conventional devices and personal opinion. Within the multicentre cohort report in this thesis, there were 33 cases of proximal migration. To identify risk factors for proximal migration a series of univariate analyses were first undertaken. Based on the univariate work, several possible risk factors were identified and these were entered into a multivariate predictive factor model.

Multivariate analysis is a statistical tool for determining the relative contributions of different causes to a single event or outcome. Within in this thesis, the contribution of multiple variables on proximal migration was considered. For all multivariate Cox proportional hazards models the 1st postoperative CT aortic neck length was found to be a risk factor for proximal migration. For every mm increase in 1st postoperative CT aortic neck length, the proximal migration hazard decreased by 10% (HR 0.90, 95% CI 0.78 to 0.98, P<0.05). Other variables were shown to be statistically significant risk factors for proximal migration, but had some dependence on the event time and statistical approach. These variables were postoperative aortic diameter changes at the caudal renal artery (HR 1.19, 95% CI 1.02 to 1.38, P=0.02), postoperative vessel length changes between the SMA and the cranial renal artery (HR 1.14, 95% CI 1.04 to 1.25, P=0.01) and the contralateral iliac limb diameter (HR 0.84, 95%CI 0.57 to 0.95, P<0.05).

Regarding, the 1st post-operative CT aortic neck length (caudal renal artery to the start of the aneurysm or changes in aortic diameter). This dominated the multivariate

analysis, being present across all event times regardless of statistical approach (e.g. SPSS versus R). The Cox proportional hazards model estimated that for every mm increase in aortic neck length, there is a 10% reduction in proximal migration hazard. This variable was also identified as being statistically significant when using univariate analysis (P=0.02). The median (IQR) aortic neck length was smaller 0 (0 to 7) mm in the proximal migration group when compared to 5 (0 to 11) mm in the non-migration group (P=0.02). Aortic neck length has been previously identified as a risk factor when using infrarenal stent-grafts (Waasdorp *et al.*, 2009). Differences in migration rates may result from the differences in the amount of apposition (area in contact) between the fabric portion of the device and the aortic wall. This may have had an effect on the overall resistance to migration by the device. For fenestrated devices, there are further considerations with regard to the aortic neck, as a risk factor. One theory surrounding aortic neck length is that it provides an indication of stent-graft to aortic wall apposition. However, if the neck length was longer for one particular group (e.g. non-migration), then this does not, necessarily prove that the device would have more contact against the aortic wall. There is the possibility that there could be a long infrarenal neck, which was highly conical and as a result, there would only be a small amount of apposition between the infrarenal aorta and the stent-graft. Another consideration would be the amount of fabric coverage directly above the caudal renal artery. If a fenestrated stent-graft was planned with four stented fenestrations, then there would be a big difference in the suprarenal fabric coverage, when compared to a device with a single unstented renal scallop. A device using a single unstented fenestration is likely to have more infrarenal aortic neck than one with four stented fenestrations and this shows that there multiple factors influencing fixation. It is important to highlight that the suprarenal fabric coverage was not

directly measured within this study. It must also be questioned why 1st postoperative neck length was a risk factor and not preoperative aortic neck length. One theory is the relatively high numbers of missing preoperative CT scans in the proximal migration group (20 out of 33). It is, however, thought unlikely that there would be a significant difference in aortic neck length between the preoperative and postoperative CT scans. As such, there may be some transferability of risk factor across to preoperative measurements. To confirm this latter point, would require additional study.

The diameter of the distal contralateral iliac limb was suggested as a further multivariate risk factor for proximal migration. A Cox proportion hazards model, using interval censoring, estimated a 16% decrease in proximal migration hazard for every mm increase in contralateral limb diameter. There are computer generated flow models, which have confirmed that the forces on a stent-graft are greater in the presence of smaller diameter CIAs (Li and Kleinstreuer, 2006a). The reason for this is that blood needs to converge suddenly into smaller iliac limbs, resulting in a significant net momentum change. Multivariate analysis did not take into consideration the proximal inlet diameter directly, this would be important in calculating the proximal/iliac ratio and any differences in displacement forces. It is also important to consider that other factors such as the type of device type (e.g. aorto-uni-iliac or tube) and whether the limbs were flared could influence the proximal/iliac ratio. The contralateral limb is likely to be the smaller diameter of the two limbs, this will have the greatest effect on the proximal/iliac diameter ratio and the resultant stent-graft drag force. This may be a reason why the contralateral side was identified as risk factor and not the ipsilateral side. When using univariate analysis, although statistically significant (P=0.02), the median (IQR) limb diameter for the proximal migration and non-

migration groups were relatively similar, 13 (12 to 15) mm versus 13 (11 to 13) mm, respectively. Although multivariate analysis suggested that patients with smaller diameter contralateral iliac limbs are more at risk of proximal migration. Clinically, there was little difference between the two groups. Further interrogation of the data revealed that the maximum contralateral limb diameter was greater in the non-migration group (28 mm) when compared with the proximal migration group (20 mm).

There can be changes in aortic morphology during follow-up, which can place a patient more at risk for proximal migration. Changes in the diameter of the aorta at the level of caudal renal artery were identified as a multivariate risk factor. For every mm increase in aortic neck diameter at the caudal renal artery during follow-up, there was an estimated 18% increase in proximal migration hazard. Similar trends can be seen in the univariate analysis, where aortic neck growth was greater in patients with proximal migration when compared to those without. There are two possible explanations for this, firstly, the inlet diameter. Unless the stent-graft is a tube with an equal inlet and outlet diameter, there will be a net displacement force acting on the stent-graft. Steady state studies have showed that the forces acting on a stent-graft increase when increasing the inlet area (diameter) (Mohan *et al.*, 2002). Patients with changes in aortic neck diameter during follow-up, therefore, are more at risk from migration, which could be the result of device oversizing or disease progression. A study by Lipski *et al.*, showed than non-stented aortic necks can increase by at least 5 mm in diameter during follow-up, in a significant number of patients (Lipski and Ernst, 1998). Regardless of aetiology, postoperative aortic neck expansion increases the stent-graft displacement force. This has also been proven for infrarenal EVAR, Cao and

colleagues used multivariate Cox regression and reported AAA neck enlargement of 10% or more as a risk factor (HR 7.3, 95% CI 1.8 to 29.2; P=0.004) (Cao *et al.*, 2002).

An increase in the postoperative SMA to cranial renal artery length was shown increase the risk of proximal migration. For every mm increase in SMA to renal artery length during follow-up there was a 14% increase in proximal migration hazard. Similar evidence was presented in the univariate analysis where length growth was shown to be significantly larger in patients with proximal migration (*P*=0.03). The median (IQR) increase in SMA to cranial renal artery length was 1.0 (-2.0 to 2.0) in patients without migration and 2.0 (-0.8 to 4.0) in patients with proximal migration. Around half of the changes within each group were between -2.0 and +2.0. The clinical usefulness of this variable is likely to be the subject of debate. For patients with proximal migration, it is hard to explain the apparent increase in SMA to cranial renal artery length during follow-up. Non-stented aortas have also been shown to have some aortic neck length growth during follow-up. The study by Lipski and colleagues reported aortic neck length growth of more than 10 mm in a significant number of patients (Lipski and Ernst, 1998). Their report was limited in that it used radiopaque surgical clips and AP and lateral abdominal radiographs to track movements. Nowadays, with the widespread available of MDCT, many would question this approach and also its lack of validation, especially surrounding with the issue of radiographic magnification. Aortic elongation has been previously suggested by Litwinski and colleagues, in their study they failed to unequivocally prove, that for some patients, the distance between the caudal renal artery and the aortic bifurcation increased (Litwinski *et al.*, 2006). Aortic elongation has been reported in in the thoracic aorta (Redheuil *et al.*, 2011) and it is, therefore, possible that focal growth could have occurred across the SMA to cranial renal artery segment. If this was the

case, then this could have resulted in an increase in distraction force on the proximal component and subsequent migration.

There were other univariate ($P<0.05$) variables tested within the multivariate Cox proportional hazards models, which did not show statistical significance. On the basis of the univariate analysis, the distance between the distal portion of the ipsilateral iliac limb and the CIA bifurcation was found to be associated with migration ($P=0.02$). The median [IQR] distance between the distal limb and the CIA bifurcation was smaller in patients without proximal migration when compared to those with evidence of migration (15 [9 to 22] versus 20 [16 to 27] mm), respectively. This link has been reported for conventional infrarenal devices (Waasdorp *et al.*, 2009, Arko *et al.*, 2005, Heikkinen *et al.*, 2006). There are, however, distinct differences with fenestrated devices in that they have separate proximal and distal bodies. Forces acting on the bifurcation are theoretically supposed to cause movement of the distal body and not the proximal fenestrated section. Observations from the study by Waasdorp *et al.*, using conventional (infrarenal) devices, identified that good iliac fixation is especially important in patients with short proximal necks (Waasdorp *et al.*, 2009). This would be even more applicable for a fenestrated series; however, none of the previously mentioned iliac fixation studies used a three part fenestrated stent-graft.

Stent-graft kinking was entered into the multivariate model (univariate $P=0.03$), but was not identified as a multivariate risk factor. For the univariate analysis stent-graft kinking, occurred at a greater rate in the proximal migration group (3 patients, 9%) compared to the non-migration group (1 patient, 1%). There were relatively low numbers of events, in both the migration and non-migration groups. Stent-graft kinking refers to stent-graft, which displayed a localised angulation of the graft or graft limb during follow-up. A similar

definition was used in the EUROSTAR report by Fransen and co-researchers (Fransen *et al.*, 2003a). It is well accepted that over the course of follow-up the configuration of a stent-graft may change. The reported incidence within the literature will depend on the type of the device, but also the relevant reporting standards used. Umscheid *et al.*, in a series of 291 patients treated with various stent-grafts over a four year period, reported kinking in 56.7% of patients. Harris *et al.*, reported on mild, significant or severe endograft kinks, reporting the latter in 10 (38%) out of 26 stent-grafts (Harris *et al.*, 1999). In the report by Fransen *et al.*, they assumed that stent-graft migration resulted in device kinking in a significant portion of patients. They also concluded that kinks are potential damaging events and that they may lead to delayed type I and III endoleaks, graft stenosis, thrombosis and conversion to open repair. The cohort within this thesis represent a series of patients with a fenestrated stent-graft implanted, it is therefore, not clear what the long term effects of fenestrated stent-graft kinking will be.

Postoperative dilatation at the level of coeliac axis was also suggested as a risk factor with univariate analysis (P=0.03). Post-FEVAR aortic neck expansion was smaller at the level of the coeliac axis (median 2.0, IQR 0.5 to 4.0 mm), when compared to the caudal renal artery (median 4.0, IQR 2.0 to 7.0 mm), in patients with proximal migration. This may explain why this variable did not reach statistical significant in the multivariate model. A biological explanation could be different levels of radial force between the two locations. This may be further explained by the general absence of graft fabric at the level of the coeliac axis. Conversely, at the renal arteries, all patients will have had the renal portion of abdominal aorta covered by fabric and a self-expanding stent-graft. These results may add to the growing body of evidence that any oversizing of the stent-graft should be used with caution.

Benjamin Howell and colleagues also argued this, confirming that the degree of oversizing determines the inlet diameter, which is subsequently the principle determinant of displacement force and can massively impact on the risk of migration (Howell *et al.*, 2005).

There were other variables that achieved univariate P values of 0.5 to 0.9. These were entered to a multivariation model and no risk factors were identified. Several of the morphological parameters have been shown to be risk factors for infrarenal stent-grafts. Questions may arise regarding their absence within this thesis. A discussion of these variables will now follow, it must be highlighted that missing values could be one explanation why some variables did not make it into a multivariate model. Zhou *et al.*, compared a standard infrarenal device to a single stented fenestrated device (Zhou *et al.*, 2007). The addition of a stented fenestration increased the force needed for initial displacement from 4.3 to 11.5 N, with a 10% device oversizing. A further, final phase of displacement then required an extra 6.4 and 16.8 N, for standard and fenestrated devices respectively. From Zhou's work, it is clear that fenestrated stent-grafts offer higher fixation when compared with standard devices. It is, however, not clear whether the fixation increases with a greater number of target vessel stents. In the cohort reported in this chapter there was a trend of less proximal migrations in patients with > 2 target vessels. Out of 121 patients without migration, 35 (29%) had more than 2 target vessel stents. When compared with the group of patients with proximal migration, less, 5 (15%) had more than 2 target vessel stents (P=0.08). When considering that almost all patients had at least a single target vessel stent, this suggests that there is some additional benefit from multiple TV stents. There is the possibly that the specific design of a target vessel stent could also influence the incidence of migration. This would have been difficult to test statistically, as these were a wide range of

target vessel stents deployed, these varied by anatomical location e.g. CA, SMA or renal and there were some trends relating to those used by individual institutions. Due to the nature of the GLOBALSTAR registry, the exact stent type was not defined in a significant number of patients. Confirming that the type of target vessel stent may not be a factor, Scurr and colleagues, in a lab experiment failed to identify any differences in the forces required to crush a Jostent, Advanta V12 or Palmaz Genesis deployed within an endograft fenestration (Scurr *et al.*, 2008b).

Zhou *et al.*, also examined the effect of oversizing on the fixation of a device. For standard devices increasing the oversizing from 5 to 10% and 5 to 20% required an extra 0.9 (27%) and 4.3 N (127%) of force for initial displacement. For a fenestrated device the extra force needed was less, 1 (9%) and 1.6 N (16%). Final displacement of a fenestrated device required an increase of 5.7 and 10.5 N, for 10 and 20% respective oversizing. For a standard device this extra force was 2.7 and 8.7 N. From Zhou's work it can been seen that the protective benefits of oversizing a fenestrated device (over 10%) are reduced in comparison with a standard device. The likely explanation for this is that most of the fixation is provided by the target vessel stent and not the interaction between the aortic wall and the stent-graft. Zhou *et al.*'s *in vitro* work used bovine aortas from which they investigated the relationship between endograft type, oversizing and the forces needed to cause displacement. The *in vivo* quantification of stent-graft oversizing in a fenestrated device is likely to be more challenging. The sealing stent is likely to oppose aortic wall over a range of aortic diameters. What may be a 20% oversizing at the SMA may reduce to 15% at the level of the renal arteries or vice versa. Device selection, therefore, requires careful consideration of these

issues, taking into account what is likely to give the best chance of a seal whilst allowing the fenestrations to align correctly.

For standard infrarenal devices morphological parameters, such as excessive neck angulation (Ghouri and Krajcer, 2010) have been associated with migration. In the cohort reported in this chapter, preoperative aortic neck diameter and coronal neck angulation demonstrated non-significant trends within the proximal migration and non-migration groups. The relationship between inlet diameter and the displacement force acting on a stent-graft has previously been discussed. The median (IQR) preoperative aortic neck diameter for patients without evidence of proximal migration was 23 (20 to 26) mm, whereas in those patients with migration the median diameter was 24 (22 to 30) mm (P=0.07). A lack of statistical significance may have resulted from the high numbers of missing preoperative CT scans, which prevented measurement of preoperative aortic neck diameter in a significant number of patients. According to the report by Howell *et al.*, the postoperative inlet diameter is likely to be more important and will be influenced by the degree of stent-graft oversizing (Howell *et al.*, 2005). This was also shown to be larger in patients with proximal migration (median 24, IQR 22 to 30 mm) when compared to those without (median 23, IQR 20 to 26 mm; P=0.07). Preoperative coronal aortic neck angulation was smaller in patients with proximal migration (median 17°, IQR 9° to 26°) when compared to a non-migration group (median 25°, IQR 13° to 38°). This factor did not reach statistical significance (P=0.06) and it is difficult to suggest a theory why migration may have been influenced in this way. Reports in the literature suggests the drag force on a stent-graft is increased in the presence of severe angulation (Li and Kleinstreuer, 2006a). The work by Li and Kleinstreuer considered a standard infrarenal device and was based on computer modelling. It is not clear how

raising the inlet into the suprarenal aorta would affect the resultant force/angulation calculations. When calculating the drag force on a stent-graft, the angle at the inlet (fabric junction) must be measured and recorded. Angulation of a fenestrated stent-graft could result in a crimping effect and this is the mechanism from which additional fixation is provided. Within the proximal migration group there was an absence of CT data in 20 out 33 patients, it is accepted that this has generated problems when forming conclusions based on these types of data.

Stent-graft design has also been linked with migration, this includes the utilisation of proximal barbs and hooks (Malina *et al.*, 1998) and stiff body devices (Litwinski *et al.*, 2006). Only a single device (Zenith fenestrated AAA stent-graft, Cook Medical) was evaluated in this thesis and, therefore, its performance against comparators remains unknown. Follow-up complications have also been shown to potentially reduce the rate of migration, Li and Kleinstreuer reported that the presence of an endoleak may mitigate the risk of stent-graft migration (Li and Kleinstreuer, 2006b). This factor has been discussed within the previous chapter, but there are further considerations to be made. Endoleaks are typically classified according to their aetiology (Chaikof *et al.*, 2002b), when referring to migration further studies may need to report the duration of the endoleak and at the same time, indicate the scale and duration of sac repressurisation, as this is likely to indicate the overall reduction in stent-graft displacement force.

Hypertension has also been reported from clinical studies as a factor (Mohan *et al.*, 2002). A computer based force displacement model by Li and Kleinstreuer (2006) clearly shows a linear relationship between systolic blood pressure and stent-graft displacement force. Understanding the clinical effects of changes in blood pressure may be difficult. It is

often difficult to categorising a patient as hypertensive, numerous definitions exist (MacMahon *et al.*, 2005) and measurements can vary depending on the circumstances in which they were acquired (Marshall, 2004). During follow-up some patients may have undiagnosed hypertension or will vary in their response to treatment (Blood Pressure Lowering Treatment Trialists *et al.*, 2008). All of these considerations would need to be factored into any formal investigation into the effects of blood pressure on endograft fixation.

The separate proximal component of the Zenith fenestrated stent-graft should theoretically help reduce the effects of the caudally directed forces experienced at the aortic bifurcation. This should help reduce the likelihood of migration to the proximal component. Agreeing with this Ziegler *et al.*,(2007) stated that the lower rate of fenestrated stent-graft migration with the Zenith device is a result of a separate proximal and bifurcation components. Although potentially helpful in opposing proximal migration, this design brings the added risk of component separation between the proximal fenestrated and distal bifurcated pieces. With the additional fixation from target vessel stents, it is likely that there would be a greater incidence of component separation instead of proximal stent-graft migration. Although not a primary focus of this study, inter-component (proximal and distal bodies) separation did occur in several patients in this series. If a 10 mm definition was used then there was a single (3%) component separation in the proximal migration group and two (2%) in the non-migration group (P=0.40). All clinical component separations were successfully managed with either the implantation of a bridging stent or using follow-up imaging. Conservative management was used if the movement had ceased and there was still good overlap between components.

There are several methodological considerations when reporting risk factors. Choice of event time definition was shown to generate some differences within the multivariate models presented. Using a numerical definition, migration will undoubtedly occur in between two adjacent CT examinations. By selecting the beginning of the interval as the event time, this is likely to be over conservative, especially if this is the first postoperative CT scan. It is thought unlikely that directly following a CT scan, the device immediately migrated 4 mm. By selecting the end of the interval (i.e. 1st CT scan when the diagnosis was made), this may be more accurate since it is guaranteed that the event had definitely occurred, even if only immediately prior to the CT scan. An alternative view is that the migration occurred between the two time points; this may be best reflected by the midpoint of the interval. It is for this reason, that interval censoring approaches have been proposed as being superior since they account for the time interval between adjacent CT examinations. When using the smaller single centre cohort data, using the midpoint most closely reflected the incidence of migration reported by an interval censoring approach. With Cox proportional hazard models, the effect of choosing a later time point e.g. midpoint or end of the interval removed several variables from the predictive factor model. This is important as the beginning of the interval is unlikely to represent the actual migration time for early points during follow-up (e.g. 1st post-operative CT scan).

The choice of statistical software is also important. There were smaller differences in the hazard ratios between the two platforms. By way of an example, there was a 2% difference in HR when using the beginning of the interval (enter technique), when switching between R and SPSS. The conclusion of this is that there must be minor differences in the approach to modelling between the two packages. When using the stepwise forward and

backward approaches, the 1st postoperative CT aortic neck length, follow-up aortic diameter changes at the caudal renal artery and length changes between the SMA and cranial renal artery are likely to be most plausible risk factors for proximal migration. Forward and backward processes cannot be undertaken with the statistical programme R, so conclusions using these techniques will have some dependence on precise migration times. If it is accepted that a Cox proportional hazards model that uses interval censored data is superior, then the two multivariate risk factors for proximal migration are 1st postoperative aortic neck length and contralateral iliac limb diameter. This would also be the case for a forward stepwise approach using the end of the interval as the event time.

As previously identified missing values are likely to influence some of the results within this chapter. The use of MI methods to compensate for missing values is a well-documented approach within the literature. The accuracy in which the MI process replaces missing values must be a primary consideration. If it can be assumed that the MI datasets provide an accurate reflection of the multicentre FEVAR cohort then the following point can be highlighted from the results. The 1st postoperative CT neck length is still a dominant risk factor for proximal migration. Aortic neck diameter change at the coeliac axis was not identified as risk factor for any of the MI datasets. Changes at the level of caudal renal artery was identified as a risk factor, this was not consistent across all MI datasets, unless an SPSS backwards approach was used (beginning or midpoint of interval as event times). Contralateral iliac limb diameter was consistent identified as risk factor across all MI datasets. There will have been situations when a contralateral limb was not deployed (tube or AUI device) and the MI process for these cases must be considered. Ipsilateral iliac limb deployment distance and graft kinking were not found to be statistically significant risk

factors for any of the MI datasets. Changes in aortic length (SMA to cranial renal artery) during follow-up, was found to be a risk factor. This was not for all MI datasets and concentrated around the beginning/midpoint of interval event times and when using an SPSS backward approach.

The bootstrapping procedure was needed to generate 95% confidence intervals for hazard ratios generated using interval censored data. Bootstrapping is a sophisticated computer processing technique that will have some dependency on the size of the sample. When generating the range of regression coefficients needed to provide an estimate of the 95% confidence intervals, the number of repetitions in the bootstrapping sequence can be specified. Too large a number of repetitions can make generation of confidence intervals impossible and too few may render them not useable. Confidence intervals generated using bootstrapping methods in this thesis used 100 repetitions. It may be possible that the 95%CI could change slightly if a different number of repetitions were selected.

Limitations

It is acknowledged that there are limitations within this chapter. One of the major limitations to this work is the number of missing values for the included cohort. This unfortunately reflects the nature of a retrospective study and difficulties in gaining access to CT data. In the UK EVAR trials, a similar core lab analysis of predictive factors for the time to first graft-related complication was made (Wyss *et al.*, 2011). Out of the 640 patients randomised to EVAR the preoperative CT scans were available and fit for purpose in 217 (34%) cases. This confirms that the retrospective access to CT data is difficult, even within a single healthcare system and with the widespread role out of PACS. There were also problems with the

completeness of data entry into the GLOBALSTAR registry. In a number of cases, clinical and device-specific variables were missing and this will impact on the overall robustness of the predictive factor analysis. It should be highlighted that missing value data were provided at regular points throughout this thesis and where possible the potential impact on outcomes discussed. It must be highlighted that any conclusions from the analysis of predictive factors must consider that this was a retrospective review of patients treated by FEVAR. This is a real-life clinical study and there were instances where preoperative CT scans, clinical and graft-related variables were not present. With respect to the preoperative CT data, there were a significant number of patients with proximal migration (20/33) that did not have a preoperative CT scan available for analysis. It is possible that there could have been more risk factors identified from this examination, if all values were present.

The effect of reporting migration as a dichotomous variable must also be considered. Migration measurements are changes in the position of the stent-graft over time. It could have been possible to investigate predictive factors by treating proximal migration as a continuous variable. This may have provided further data on the effects of different variables on the magnitude of migration. A decision was made not to treat migration as a continuous variable, this was because of the uncertainty surrounding the accuracy of migration measurements below 4 mm.

There are a number of publications, which have discussed the number of variables that can be assessing in a multivariate model (Peduzzi *et al.*, 1996, Yuan and Lin, 2006). Different theories exist regarding the overall size of the cohort and the number of outcome events needed per included variable. There were a total of 33 proximal migrations in the multicentre cohort. This will have generated some issues with regard accuracy of the

multivariate analysis and the reliability of the resultant regression coefficients and confidence intervals. The multivariate analysis of proximal migration of infrarenal stent-graft has been previously conducted with fewer patients and fewer events (Cao *et al.*, 2002). This does not imply that the methods used by Cao *et al.*, are correct, but data presented in this thesis are the first if its kind and will help move forward the investigation of fenestrated stent-graft migration.

7.5 Conclusions

Using a multivariate analysis, 1st postoperative CT aortic neck length has been consistently identified as a risk factor for proximal fenestrated stent-graft migration. Other risk factors, which must be considered, include the contralateral iliac limb diameter, postoperative changes in the aortic diameter at the level of the caudal renal artery and changes in the SMA to cranial renal artery length. The inclusion of risk factors other than 1st postoperative neck length will have some dependence of the event time definitions used and individual Cox regression modelling processes. Other variables were suggested from the univariate analysis, but were not included in the resultant multivariate model. This may be, in part, explained by a large number of missing values, especially those that would have been obtained from preoperative CT scans. Based on data reported in this chapter, there are identifiable risks factors for proximal migration and the clinical utility of these must be carefully considered. Fenestrated repair is a complex process, up until now the majority of devices were custom made. As such there is a significant amount of variation within each individual stent-graft; this has also made identifying clinical significant parameters more difficult. Lessons can be learnt from the data presented within this chapter, the identification of risk factors is complex, especially when using retrospective imaging data. It

is important than further work is undertaken is order to better understand the migration of fenestrated aortic stent-grafts.

8. Discussion, further research and conclusions

8.1. Summary of results

This thesis has four aims. The first aim was to validate a CT central luminal line (CLL) measurement technique for the quantification of aortic stent-graft migration. Using this validated CT CLL technique the second aim of the thesis was to report the incidence and timings for the migration of fenestrated stent-grafts, both at the proximal and distal landing zones. The third aim was to report any related sequelae (complications and reinterventions) for cases of proximal and distal migration. The forth aim was to investigate the predictive factors for proximal migration of fenestrated aortic stent-grafts. A tabulated summary of the main results are presented below in Table 8.1 and Table 8.2. The multicentre incidence and timings for migration of the Zenith fenestrated AAA stent-graft are presented in Table 8.1. The predictive factors for fenestrated stent-graft migration are presented in Table 8.2.

Table 8.1 A summary of the freedom from proximal and distal (iliac) limb migration

	Proximal migration			***Any iliac limb migration***		
Time, mo	**n. risk**	**survival**	**95% CI**	**n. risk**	**survival**	**95% CI**
12	89	82%	75% to 89%	83	85%	79% to 92%
24	49	77%	70% to 85%	45	82%	75% to 90%
36	31	77%	70% to 85%	22	65%	52% to 80%
48	13	64%	51% to 80%	12	65%	52% to 80%

Survival estimates using interval censored data. CI, confidence interval. Mo, months.

Table 8.2 A summary of multivariate risk factors identified using a Cox proportional hazards model. Entry into the model require a univariate P value <0.05.

Covariate	HR	95% CI	R	SPSS Forward Stepwise			SPSS Backward Stepwise		
			Interval censoring	Beginning	Midpoint	Endpoint	Beginning	Midpoint	Endpoint
Ipsilateral CIA deployment distance, mm#	1.02	0.97 to 1.06							
Contralateral iliac limb diameter, mm*	0.84	0.57 to 0.95	✓			✓			
1st postop CT aortic neck length, mm*	0.90	0.78 to 0.97	✓	✓	✓	✓	✓	✓	✓
Postop aortic diameter change, coeliac axis, mm#	1.01	0.81 to 1.21							
Postop aortic diameter change, caudal renal artery, mm	1.18	1.02 to 1.38			✓		✓	✓	
Postop length change, SMA to cranial renal artery, mm	1.14	1.04 to 1.25			✓		✓	✓	
Graft kinking#	0.61	0.0 to 3.40							

HR, hazard ratio. CI, confidence interval. HR were reported using the R programme and interval censored data where statistically significant*. If not statistically significant in R, HR were reported for the any other approaches, where P <0.05 with the HR closest to 1 reported. Variables not statistical significant risk factors for any approached were highlighted with#.

Aim 1: Validation of CT CLL migration measurement technique (Chapter 4)

Using aortic phantoms the mean difference in the CT CLL migration between the actual and observed measurements (estimate of bias) was +0.4 mm (95% *limits of agreement*: -2.5 mm to + 3.3 mm). The 95% *limits of agreement* for measurements both within and between observers were -2.1 mm to + 2.1 mm and -2.4 mm to + 3.3 mm, respectively. Data from the phantom study generated a Coefficient of Repeatability (RC) of 2 mm for the within-observer

measurements. This is the value below which the difference between repeat measurements are expected to lie with a 95% confidence. When using clinical CT data from patients with a selection of aortic stent-grafts implanted, 95% *limits of agreement*, within and between observers was -2.6 mm to +3.1 mm (RC = 3 mm) and -3.5 to +3.9 mm, respectively.

Overall the results from the validation experiment demonstrated that the bias from CT CLL migration measurements is small and insignificant from a practical point of view. A small amount of measurement variability, both within and between observers does exist. It should, however, be feasible to detect changes in stent-graft position during following which are ≥ 4 mm. On this basis, stent-graft migration (both proximal and distally) was defined as movement during follow-up ≥ 4 mm.

Validation of the CT CLL measurement was undertaken using a commonly performed vascular CT protocol. If when using a CT CLL technique, the CT protocol was significantly different to that used in the validation experiment, then the subsequent bias, variability and migration definition would need to be reconsidered.

Aim 2: Incidence and timings of proximal and distal (iliac) migration of the Zenith fenestrated AAA stent-graft (Chapters 5 & 6)

Using retrospective CT data from nine UK centres migration of a Zenith fenestrated AAA stent-graft was assessed in 154 patients. Median follow-up for the study cohort was 20.9 (IQR 10.4 to 26.5) months. Estimations of freedom from proximal migration, using Kaplan-Meier survival analysis with interval censoring, at 12, 24, 36 and 48 months were 82% (95% CI 75 to 89), 77% (95% CI 70 to 85), 77% (95% CI 70 to 85) and 64% (95% CI 51 to 80), respectively. Distally, estimations of iliac migration free survival were 85% (95% CI 79 to 92),

82% (95% CI 75 to 90), 65% (95% CI 52 to 80) and 65% (95% CI 52 to 80) at 12, 24, 36 and 48 months, respectively. All migrations at the proximal landing zone were caudal in direction; median migration was +6.0 mm (range, +4.1 to +10.0 mm). Migrations at the distal landings zones were all in a cranial direction, median migration was -6.1 mm (range, -21.3 to -4.1 mm).

Aim 3: Complications and reinterventions in patients with proximal and distal migration of the Zenith fenestrated AAA stent-graft (Chapters 5 & 6)

A variety of FEVAR-related complications were present in patients with and without CT evidence of migration. With regards to the multicentre cohort within this thesis, there were no statistically significant differences in graft-related endoleaks, between the migration and non-migration group (P=0.15). Although non-significant, there was a doubling in the incidence of type II endoleak in the non-migration group (14%) when compared to the proximal migration group (6%). Target vessel losses were relatively evenly distributed between patients with (9%) and without (8%) evidence of proximal migration (P=0.35). At the distal (iliac) landing zones, there was a general lack of iliac-related secondary events. There were six limb occlusions, five were in the first 30-days and not attributed to any device migration. Distal type I endoleaks occurred in one (0.6%) patient without any evidence of migration.

Also in the multicentre cohort, there were 13 reinterventions in 13 (8%) patients for either endoleak or target vessel compromise. There were no statistically differences in the reintervention rates between patients with and without CT evidence of proximal migration (P=0.50).

Using a log-rank test and interval censored data, there were no statistically significant differences in the incidence of proximal migration, in patients with and without complications (P=0.84) and reinterventions (P=0.81).

Aim 4: Predictive (risk) factors for proximal migration of the Zenith fenestrated AAA stent-graft (Chapter 7)

A predictive factor analysis was undertaken using data on the incidence and timings of proximal migration together with a selection of pre-, intra- and postoperative variables. The resultant analysis consisted of univariate and multivariate methods (see Section 7.3).

Multivariate analysis, using a Cox proportional hazards model identified the 1st postoperative CT aortic neck length as a risk factor for proximal migration (HR 0.90, 95% CI 0.78 to 0.97; P<0.05). The identification of other risk factors for proximal migration were dependent on the choice of event time definition and statistical approaches. The 1st postoperative CT aortic neck length was found to be a risk factor in all of these scenarios. Hazard ratios estimated that there was around a 10% decrease in the proximal migration hazard for every mm increase in aortic neck length. If different event time definitions and modelling approaches were used, then postoperative changes in aortic diameter, at the level of the caudal renal artery (HR 1.22, 95% CI 1.03 to 1.44; P=0.02), was the second most likely predictive factor to be included in the model. Other predictive factors identified include contralateral iliac diameter (HR 0.84, 95% CI 0.57 to 0.95, P<0.05) and postoperative changes in SMA to cranial renal artery length (HR 1.12, 95% CI 1.01 to 1.24, P=0.02).

Univariate analysis did suggest further, possible, risk factors (P<0.05), but following multivariate analysis these were not found to be statistically associated with proximal

migration. These additional variables, identified in the exploratory (univariate) analyses, were ipsilateral iliac limb deployment distance from the CIA (P=0.02), postoperative change in aortic diameter at the coeliac axis (P=0.03), postoperative changes in the length between the SMA and the cranial renal artery (P=0.03) as well as stent graft kinking (P=0.03). A study with a larger sample size and fewer missing values will increase the certainty about the role of these factors in proximal migration of fenestrated aortic stent-grafts.

Within the risk factor analysis, there were a series of missing values for some variables. These were highlighted within the thesis and multiple imputations methods used to account for missing values. The additional modelling of missing data, made only minor changes to the multivariate predictive factors model. One exception was that the contralateral limb diameter had more of a significant role in models generated using MI. For this to be considered a valid risk factor, a detailed understanding of the missingness mechanisms and decisions within the multiple imputation process are needed.

8.2. Methodology and limitations

CT CLL quantification of aortic stent-graft migration (Chapter 4)

Up until now, there have been no robust techniques for measuring stent-graft migration in the abdominal aorta. For conventional (infrarenal) stent-grafts, there are well recognised definitions for stent-graft migration and these are contained within the relevant reporting standards (Chaikof *et al.*, 2002a). These definitions are not appropriate for fenestrated stent-grafts, where smaller movements could be catastrophic. Over recent years, concerns about the migration of fenestrated stent-grafts had arisen within the vascular community. Despite this concern, to date no validated measurement techniques have been developed or suitable

definitions proposed. Studies investigating stent-graft migration are generally retrospective in design. Rather than to propose a new definition for fenestrated stent-graft migrations, it was important to understand what definitions could be achieved using current CT technology. The first phase of this thesis was to investigate the accuracy of a CT CLL technique in quantifying stent-graft migration. It was thought likely that this technique would the most precise migration measurement option. Some would consider this questionable, as there are other techniques available for undertaking length measurements using CT images. A broader study would have been to quantify stent-graft migration, using a series of different CT measurement techniques, and then compare the results. The decision to evaluate a single technique (CT CLL), within Chapter 4, was guided by evidence from the literature (O'Neill *et al.*, 2006b) and the resources needed to complete this part of the thesis (Ghatwary *et al.*, 2012). CT CLL techniques have been used previously to quantify stent-graft migration in the thoracic aorta, these techniques and also commonly used to measure the length of tortuous and angulated vessels within the abdomen (Ota *et al.*, 2005, Rengier *et al.*, 2009).

Currently, there is no gold standard for reporting the position of a stent-graft within a patient. Medical imaging examinations can provide an estimation of the position but, there are no safe methods for confirming the exact position of a device. With this in mind, two commercially available stent-grafts were deployed in a series of plastic aortic phantoms and subject to CT examinations. The phantoms were then displaced and subject to a second CT scan. Visual differences between the two positions of stent-graft were considered to be actual migration, differences between the two CT scans were considered to be an estimate of the CT migration. The use of a plastic phantom has raised several methodological issues.

There was an absence of diameter and angulation changes within the plastic aortic phantoms, this prohibited the testing of the CLL technique across a range of morphologies. Phantom CT images also differed from *in vivo* images in that there were no other organs, normal variants, vascular calcification or thrombus within the images. This may have generated difficulties with fidelity and when undertaking migration measurements. Alternatives could have been to use animal or cadaveric models. The funding source prohibited the use of animals within this thesis. Cadavers would have created logistical difficulties, including the access to body parts and their transfer to a CT scanner. In retrospect, the process for producing the plastic models could have included models with varying levels of angulation and diameters. A step further would be phantoms designed from individual CT data. This would be in the realms of further research as this would have increased the number of measurements needed and the overall length of the study.

The variability for stent-graft migration measurements both between and within observers was also a concern. For the CLL validation study observers were required to have previous experience in assessing migration. In additional, each observer was provided with study specific training and had practice attempts, using the CT CLL technique, on a separate of test datasets. A key step in the measurement process was the identification of vascular and device-specific landmarks. Some landmarks may be more easily visualised on CT than others, the choice of which, could influence measurement accuracy and variability. Studies have shown improvements in measurement variability when precise definitions are used (Oshin *et al.*, 2010). Further improvements have been demonstrated when automated computer techniques are used to acquire measurements from CT data (Wyss *et al.*, 2009).

Within this thesis, landmarks tested as part of a validation experiment were consistently applied throughout subsequent chapters.

In addition to the phantoms, the CT CLL technique was also tested on clinical follow-up CT datasets. Methodological considerations now relate to the choice of device, number of patients evaluated, range of migrations encountered and the quantity and experience of the observers. Talent and Zenith stent-grafts were selected for the evaluation of the CT CLL technique. At the time of the study they were the two most common aortic stent-grafts implanted (Brown *et al.*, 2007). Over recent years, the Talent has been replaced by the Endurant and there have been some modifications to the structure of the Zenith stent-graft. Other devices, such as the Anaconda and Excluder, are now more frequently used within clinical practice. Each device has variations in metallic composition, structure of the proximal and distal landing zones, all of which could affect the visibility of key landmarks and subsequent migration measurements.

Measurement from CT scans can be a lengthy process. Clinical observers will only have a limited amount of time available and the study must be achievable within a reasonable time frame. These factors help form the basis for the sample size used in the validation experiment. There was also the risk that patients selected for inclusion in the clinical phase of the validation study may have no (or only very small) levels of migration. This situation would affect the overall range of migrations that the CLL technique was tested across. This was not a problem within this thesis where a range of migrations both in the phantom and clinical CT scans were tested.

Assessment of the incidence, timings and related sequelae for migration of a fenestrated stent-graft (Chapter 5 & 6)

Using definitions from the validation experiment (Chapter 4), follow-up CT scans of patients treated with a Zenith fenestrated AAA stent-graft were evaluated for the presence of proximal or distal (iliac) stent-graft migration, using a CT CLL technique. To the author's knowledge, this was the first study to evaluate stent-graft migration using clearly stated definitions, event times and a validated technique. There were further advantages to the study design. 1) methods were initially piloted using a single centre cohort, 2) all patients had the same stent-graft implanted (Cook Zenith fenestrated) 3) treatment criteria, implantation procedures and follow-up were relatively similar 4) evaluation of migration was by a single centralised centre 5) further analysis used mid-sized multicentre cohort of patients who had CT scans available in DICOM format. There were additional advantages to the overall analytical approach used within the key outcomes. Survival analyses used an interval-censoring approach to account for the lack of certainty regarding precise timing of migration (between two adjacent CT scans). In order to report complications the study had access to imaging data and records submitted to a UK fenestrated stent-graft (GLOBALSTAR) registry.

There were several possible limitations to the study design. Identification of migration was, following validation, by a single observer in a centralised image analysis laboratory. It would have been useful for each site to independently assess migration on its own patients. These figures could then have been compared against migration rates reported by the core lab. This would provide an indication of the generalizability of the CT CLL technique for routine migration reporting. A further limitation may also be the structure

of the core lab itself. Currently, there are attempts by industry and academic leaders to demand the reporting of core lab quality-control measures (Brinjikji and Kallmes, 2012). More and more trials are being conducted using a core lab, it is likely that fenestrated stent-grafts will be subject to further scrutiny, possibility using core lab facilities. If a core lab is used then it should be clearly stated what role the core lab will play and the quality control standards that will be in place. The issue of missing patients and data (iliac CLL assessments) have been discussed at length within this thesis. The limitations of a retrospective study design are also well cited within the literature (Hess, 2004). One major limitation of any retrospective study is the quality of data reporting and managing those patients who are lost to follow-up. With the widespread role out of PACS and the electronic patient record, one may think that we are at a point when retrospective data collection would be easier. Registries now provide an option for data capture, but they too are subject to data quantity and completeness issues. Prospective trials may be the solution, ethics and institutional approvals will then be sought prior to the commencement of the study. Financial measures are also usually in place to order to support any additional data collection mechanisms (e.g. CT scan transfers). The internet also provides options for the collection of imaging data. Successful retrospective studies have been conducted, using a medical imaging repository, at M2S, Inc. (West Lebanon, NH). At this facility, using standard algorithms, M2S has created three-dimensional computer models from CT images of AAA pre- and post-repair. Images were sent by secure link, directly following acquisition on the CT scanner, they were then mass post-processed. By way of an example, Schanzer *et al.*, reviewed CT scans submitted to M2S from 1999 to 2008 and this included data from 10,228 patients (Schanzer *et al.*, 2011).

Further review of outcomes using fenestrated stent-graft may be best served using a central image repository.

The 1st postoperative CT scan was considered as the baseline in order to track the position of the stent-graft over time. In many instances, this was performed within the first 30-days following implantation. The cut off point for patients included in this thesis was a scan within the first 6-weeks. Questions may arise regarding any migration, which may have occurred before the 1st postoperative CT scan. For infrarenal AAA, there have been cases of migration either intra-operatively or within the first few days following repair. These devices, however, do not have additional fixation from target vessel stents and fabric deployed in the suprarenal aorta. It is possible that some early migration may have occurred and that a more accurate understanding of migration may have been gain using post-discharge CT scan. In some centres, flat-panel fluoroscopy systems can acquire CT images at the end of the implantation procedure. These are usually limited in quality but may provide a more reliable indication of the implantation position of the stent-graft. It is worth highlighting that all of these applications require the use of ionising radiation. Data collected in this study was part of the standard care of the patient and did not expose them to any additional risks from ionising radiation or nephrotoxic iodinated contrast.

The follow-up period of patients included within this thesis must be also considered. Many believe that migration is a relatively late occurring complication and that a minimum follow-up period must elapse before reporting outcomes. A report by Cao and colleagues, who investigated migration of the Medtronic AneuRx device, stipulated in their methods section that a minimum follow-up period of 2 years was required (Cao *et al.*, 2002). Consideration must be given to those patients who may have had stent-graft migration but

did not achieve 24-months follow-up (e.g. lost to follow-up, died or converted to open repair). Within this thesis, 62 (42%) of patients had follow-up greater or equal to 2 years. Any interpretation of migration or complications, must take into consideration the follow-up data available. There is the option of designing a further study that would recruit, based on a minimum number of events. Data from this thesis will provide an indication on the time requirements for such a study. Such an approach may increase the power of any analysis of risk factors.

There was some heterogeneity in the stent-graft devices implanted in the thesis cohort. Zenith fenestrated stent-grafts are custom-made devices and there can be variation in the number and types of fenestrations, number of sealing stents and the types of target vessel stent used to secure fenestrations. There are further options of bifurcated, AUI or tube devices and there may have adjuvant procedures during deployment (e.g. balloon moulding that may influence overall outcome). There is now the option of 'off-the-shelf' fenestrated devices and these may make comparisons simpler. The results in this thesis are based on a single device, the Zenith fenestrated AAA stent-graft (Cook Medical Inc, Bloomington, IN). Vital performance data is now available for the commonest fenestrated stent-graft to be implanted. There are, however, several new devices, which are commercially available (i.e. Ventana, Anaconda fenestrated) and have significant design variations, the results of this thesis will not be generalizable to these devices but will provide data from which to compare future performance.

Predictive factors for fenestrated stent-graft migration (Chapter 7)

From this thesis, multicentre data are now available reporting migration of fenestrated aortic stent-grafts. The focus now turns to the identification of predictive factors for migration, which are also novel. There are several reasons for this gap in the literature, there have been no previous clinical studies investigating predictive factors for the proximal migration of fenestrated stent-grafts. Studies that have investigated the migration of infrarenal stent-grafts are case-matched single centre series. The analysis of risk factors in this thesis, unlike reports from the EUROSTAR registry, is focused on a single device and a relatively homogeneous cohort of patients. A further advantage of this predictive factor work is that modelling for risk factors included, whether the event had taken place in addition to the event time. Further attempts were made to model uncertainties, regarding the precise event time, by using interval censored data. Variables collected within the predictive factor analysis were also wide, there was no pre-specification of only a small set of risk factors prior to the start of the study. By contrast, the UK EVAR trial examined a limited set of variables, relating to the attachment sites and the time to first graft-related complication (Wyss *et al.*, 2011). The influence of thrombus, calcification, angulation and tortuosity were investigated but it was not clear why morphological factors (e.g. aortic neck diameter and length) were not included in their multivariate analysis. A further strength of this thesis was that statistical modelling used a multivariate approach, in order to ascertain the contribution of multiple risk factors on the risk of migration.

There are, however, a series of methodological limitations to this chapter of thesis. Firstly, the sample size and number of migration events. This is one of the few multicentre cohorts, with more than 100 patients, to report any FEVAR outcomes. However, when

compared to standard EVAR series and other open vascular surgery publications, this is a relatively small sample size. The number of migration events are also important, whilst it is encouraging that the number of proximal migration events are small, this generates difficulties when investigating risk factors, especially when using multivariate analysis. Two similar predictive factor studies (using standard EVAR device), both by Thomas Wyss and colleagues, were analogous in design. One study investigated six covariates, when there were 53 complications (Wyss *et al.*, 2011) and four covariates, when there were 27 events (Wyss *et al.*, 2010).

Missing patients and risk factor data were also a problem, the extent of which could not be known when planning this thesis. Difficulties stemmed from missing values in the GLOBALSTAR registry and missing preoperative CT scans for some patients. To overcome this, an option could have been for each participating centre to provide an assessment of preoperative AAA morphology, on all submitted patients. At the same time, study data entry sheets could be completed for all eligible patients, by the participating centre. There could, however, have been problems with these two approaches. A constant theme amongst Trust research offices were any costs associated with research. If a participating centre was asked undertake additional work, the lead site would be approached for reimbursement. By way of an example, the transfer costs for a CT scan, ranged from £10 to £150. If a local researcher was required to undertake CT measurements or obtain data from case notes, then this would have required additional reimbursement. These problems were not initially perceived when designing data collection methods within this thesis, as such there was no funding allocated within the NIHR research grant. Even if monies were available, there would be training requirements for observers to undertaking CT measurements. It may also have been

possible that some variables were missing from case notes. If this were the case, then there would still have been missing data. Perhaps, the only real way forward would be a prospectively designed study, appropriately resourced and linked with a central image core lab repository.

8.3. Interpretation of results

Overall, the results of this thesis indicate that the migration of a fenestrated stent-graft does occur during follow-up. Migration can occur at both the proximal and distal (iliac) landing zones, but is not associated with a higher incidence of complications or reinterventions. The identification of risk factors for fenestrated stent-graft migration can have benefits to patients, clinicians and manufacturers. An in-depth discussion on the interpretation of the results formed a key element within of each of the chapters. It must be made clear, that there are many novel findings and contributions from this thesis.

The novel findings in this thesis are: (i) a validated technique for the assessment of stent-graft migration, (ii) data on the incidence, timings and related-sequelae for proximal and distal migration of the Zenith fenestrated AAA stent-graft, and (iii) predictive factors for the proximal migration of fenestrated stent-grafts. This thesis presents for the first time (iv) a definition of stent-graft migration, which is based on an experimental analysis of routine CT techniques and commercially available stent-grafts. Moreover, presented here for the first time is (v) the incidence, timings and related-sequelae for migration of the Zenith fenestrated AAA stent-graft, using robust definitions and assessment techniques. This thesis also contributes to the literature in this field, by allowing for the first time (vi), the comparison of migration rates and timings between studies. This thesis also provides the first (vii)

assessment complications detected using serial CT examinations, which are reported using interval censored survival analysis. This technique accounts for the uncertainty in event time between adjacent CT scans. Such an approach would be also applicable to other complications such as component fracture, kinking, target vessel loss and endoleaks, which can occur asymptomatically between two time points. This thesis also contributes to the literature in this field, by showing for the first time (viii) risk factors for proximal stent-graft migration.

8.4. Suggestions for future research

Future research will fall into two categories: the identification of stent-graft migration and the reporting of risk factors. For the identification of stent-graft migration, other projects have already been suggested with this thesis, which investigate a series of additional factor that may be associated with CLL measurement accuracy and variability. These are likely to include differences between computer software packages, individual CT protocols and differences which may result from variation in AAA morphology. New investigations into the assessment of stent-graft migration must consider using a current range of commercially available stent-grafts. These will have individual device-specific landmarks, which must be factored into the study design. Work is needed to identify alternative measurement techniques, which will not exclude a significant number of patients because of technical variations (e.g. iliac limbs with IIA occlusions or unenhanced CT scans). Measurements from CT data can also be prone to observer variability and can take time. Consideration should be made to investigations of automated migration measurement techniques. They may provide greater measurement accuracy and could be applied within each participating centre, thus avoiding problems with data transfer agreements, observer training and variability.

Further work is needed in order to provide more evidence surrounding the predictive factors for fenestrated stent-graft migration. In this thesis, conclusions were limited because of a large number of missing CT scans and data within the GLOBALSTAR registry. Further studies must consider methods to ensure greater compliance. This may be from a prospective trial, although follow-up would need to be long enough and resources in place to collect data across the whole duration of the study. One option would be that professional bodies take the lead in designing and delivering national registries. These must have the necessary permits and mechanisms for robust data collection. The National Vascular Database within the UK has a good history of capturing surgical outcomes across the UK. Many clinicians believe that it is a professional obligation to audit practice and this may need to evolve to monitoring more widespread outcomes. Device manufacturers also have an obligation to facilitate the collection of this information. Difficulties can arise when attempting to negotiate international boundaries. Before approving a drug or medical device within the US, the FDA can request additional data collection and analyses. This should be a consideration within the UK, before a device is approved for investigational use there should to be clear data collection methodologies in place for monitoring outcomes.

A final option for research is into new technologies. Durability has always been a concern following EVAR. Manufacturers are now starting to move to alternative devices, which are no longer based on a fabric covered metal skeleton. For example, the Nellix device uses bilateral stents and an endobag filled with a biostable polymer. This new concept of endovascular aortic aneurysm sealing (EVAS), avoids the complications of collateral perfusion and achieves fixation from total anatomic apposition. This device is thought to be novel and will avoid migration and its related complications. This can only be proven with careful

evaluation, using appropriate migration assessment techniques, which is tailored to the specific device and has sufficient follow-up.

As previously discussed within the thesis, MDCT take a snapshot of a stent-graft deployed in a pulsatile vessel. New techniques are now available, which can imaging the aorta during the cardiac cycle and will provide information of stent-graft movement during a heartbeat. Further investigation into this area may improve the accuracy of stent-graft migration measurements and also allow greater understanding of which patients may encounter complications from stent-graft migration.

MDCT has been used to follow-up patients after both EVAR and FEVAR. The costs associated with follow-up have impacted on the applicability of endovascular repair. For conventional stent-grafts, there has been a trend towards surveillance using ultrasound and abdominal radiography, instead of MDCT. If this trend moves across to FEVAR devices, then there will need to be validate methods for measuring stent-graft migration using abdominal radiography.

8.5. Conclusions

Fenestrated aortic stent-grafts continue to provide a valuable treatment option for patients with AAA, who are not amenable to open surgery. Endovascular techniques, such as fenestrated aortic stent-graft repair, are now the dominate management option but are not without complications. The lower 30-days mortality rates associated with aortic stent-grafts still requires a careful balance against the need for life-long surveillance and the increased possibility of complications. For fenestrated repair, concerns regarding the possibility of device migration have stemmed from reports involving infrarenal devices and the theoretical

possibility that even small movements could be potentially catastrophic. Findings presented in thesis confirm that migration of a fenestrated stent-graft can occur, both at the proximal and distal landing zones. Results from this thesis are unlike reports for infrarenal stent-grafts, in that there appears to be a low complication and reintervention rate associated with fenestrated stent-graft migration.

This thesis sheds light for the first time on the need for an appropriately validated migration assessment technique (Chapter 4). Understanding and comparing migration rates within the literature has been problematic. Measurement techniques are usually absent or poorly documented and definitions can vary between reports, often without justification. The assessment of subtle changes in stent-graft position is complex, factors influencing the accuracy and variability of measurements are likely to include the measurement technique, imaging protocol, AAA morphology, type of device and experience of the observer. Findings presented in this thesis will hopefully raise awareness within the vascular community, that there must be robust migration assessment techniques and the relevant quality-control mechanisms must be clearly stated within any outcome data.

When assessing stent-graft migration using a CT CLL, the estimated bias is small and insignificant from a practical point of view. This thesis provides confidence that a CT CLL technique provides an accurate reflection of any changes in device position. Observer variability was also a consideration and was tested in phantom and on human CT datasets. Minor measurement variability both between and within observers exists and this should also be factored into any clinical decision making. This thesis has demonstrated that when using 2 mm MDCT scans, it is feasible to detect stent-graft positional changes which are ≥ 4 mm. It is important to stress that a CT CLL analysis should not be used in isolation. If

migration is suspected, then a full and detailed evaluation using all CT imagery must be implemented. This latter point is important as it will help evaluate issues such as the presence of related complications, focal elongation and allow the consideration of possible management options.

Initial pilot work reported in this thesis, based on a single centre sample of fifty-five patients, demonstrated that migration at the proximal and distal landing zones occurs in around a quarter of patients by four years. The majority of migrations are less than six millimetres in length, however, movements greater than ten millimetres were reported at both the proximal and distal landing zones. Despite this, migration still appears to take a relatively benign course. In order to have a greater understanding of this phenomenon, further analysis of a larger number of patients and migration events are required. Evaluation of fenestrated stent-graft migration with a larger, multicentre cohort (154 patients, nine centres) confirmed that migration at the proximal landing zones occurs in around a third of patients by four years. The incidence of proximal migration peaks twice, once during the first year after repair and a second between years 3 and 4. This early peak raises the issue of barb engagement into the aortic wall and mirrors data reported using lab-based studies. Results presented in this thesis are encouraging in that proximal migration does not appear to be significantly associated with proximal type I endoleak or target vessel loss.

Iliac limb migrations showed a similar incidence to proximal migration. This incidence peaked between years 2 and 3 and a third of patients had at least one iliac limb migration by 4 years. As with proximal migration, iliac related complications and reinterventions were rare. Assessment techniques are, however, needed that can access iliac limb migration in the presence of an occluded internal iliac artery.

Concerns still exist regarding any post-EVAR rupture and whether there will be any association with migration. Several ruptures have been reported for FEVAR, none from this thesis. At present there is no evidence to suggest that post-FEVAR rupture is related to migration, however, studies involving a greater number of patients with longer follow-up are required. Since migration can occur at any time point, routine follow-up imaging is recommended.

This thesis establishes the incidence of proximal migration for fenestrated stent-grafts. This focus must now turn to the identification of risk factors. Establishing risk factors could inform patient selection, allow improvements in stent-graft design or allow follow-up strategies to be tailored to individual risk profiles. A shorter 1st postoperative CT aortic neck length has been consistently identified as a risk factor for proximal fenestrated stent-graft migration. Other risk factors, which must be considered, include the contralateral iliac limb diameter, postoperative changes in the aortic diameter at the level of the caudal renal artery and changes in the SMA to cranial renal artery length. As previously stated the inclusion of risk factors other than 1st postoperative neck length can have some dependence of the event time definitions used and individual Cox regression modelling processes. Other variables were suggested using univariate analysis but were not included in the resultant multivariate model. This may be, in part, explained by a large number of missing values, especially those that would have been obtained from preoperative CT scans, further research in this area is, therefore, warranted. Based on data reported in this chapter, there are identifiable risks factors for proximal migration and the clinical utility of these must be carefully considered.

9. References

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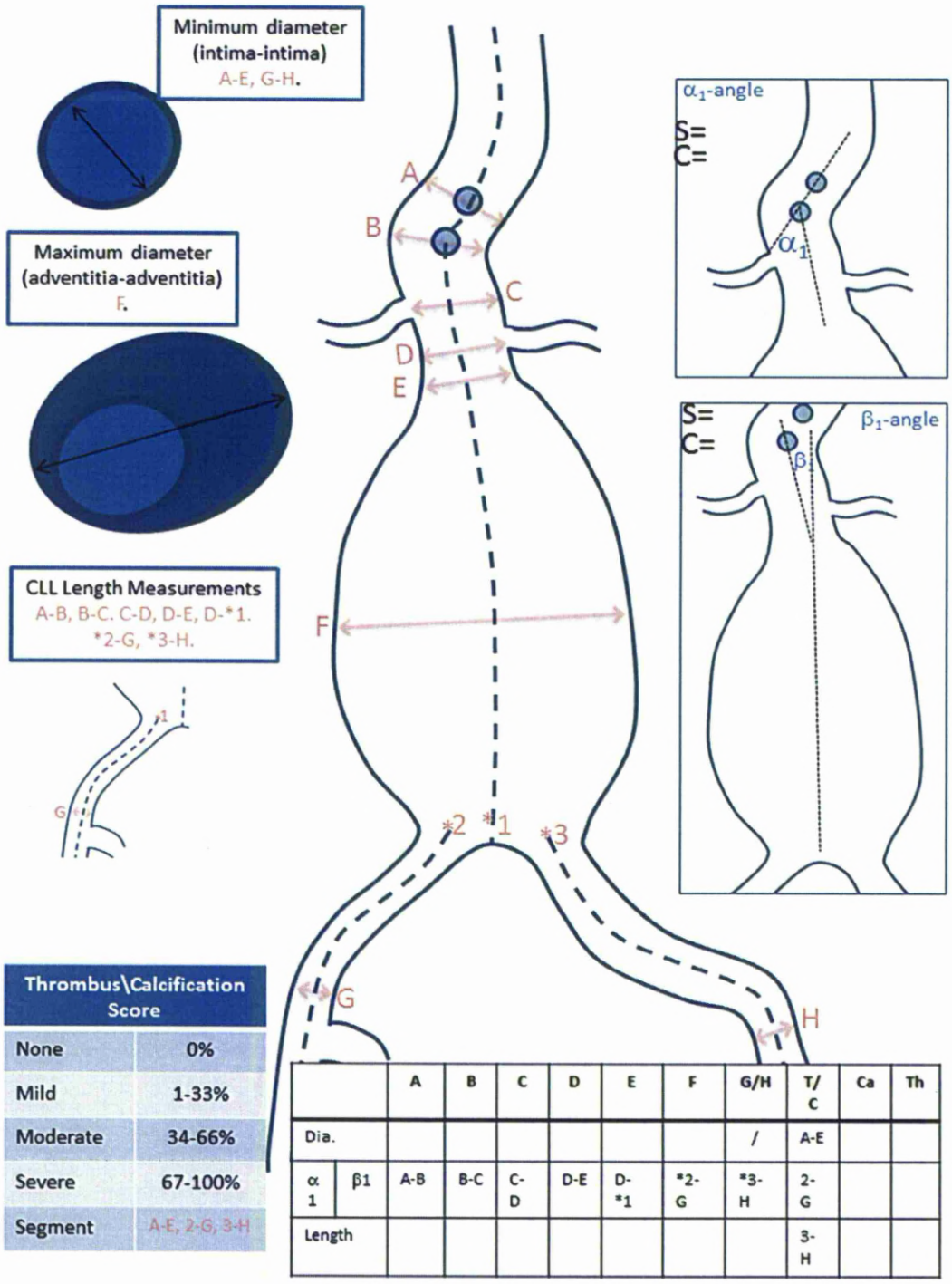
10. Appendices



Thrombus\Calcification Score	
None	0%
Mild	1-33%
Moderate	34-66%
Severe	67-100%
Segment	A-E, 2-G, 3-H

	A	B	C	D	E	F	G/H	T/C	Ca	Th
Dia.							/	A-E		
α1 β1	A-B	B-C	C-D	D-E	D-*1	*2-G	*3-H	2-G		
Length								3-H		

APP_1 Summary statistics for demographic, clinical and pre-operative morphological factors (continuous variables)

Baseline characteristics		n	Missingness n, %	Normality test, P value	Mean	SD	Median	IQR	Min, Max
	Age (years)	151	3, 2%	0.062	73.9	6.8	74.0	69.0 to 79.0	54.0, 87.0
	Body mass index (kg/m^2)	95	59, 38%	<0.001	27.8	4.5	26.8	25.1 to 30.6	19.1, 45.4
	Heart rate (beats per minute)	105	49, 32%	0.003	71	13	70	61 to 81	48, 112
	Systolic blood pressure (mmHg)	105	49, 32%	0.016	142	23	140	125 to 152	92, 208
	Serum haemoglobin (g/dl)	109	45, 29%	0.003	13.8	1.6	13.9	13.0 to 15.1	9.5, 16.6
Pre-operative CT scan									
Diameters, mm	Coeliac axis (CA)	94	60, 39%	0.059	25.6	2.8	26.0	24.0 to 27.0	19.0, 34.0
	Superior mesenteric artery (SMA)	95	59, 38%	0.107	24.3	2.9	24.0	22.0 to 26.0	18.0, 33.0
	Cranial renal arteries (CrRA)	95	59, 38%	0.077	23.6	3.6	23.0	21.0 to 25.0	16.0, 33.0
	Caudal renal arteries (CaRA)	94	60, 39%	0.015	23.7	4.4	23.0	21.0 to 26.0	14.0, 38.0
	Bottom aortic neck (BN)	95	59, 38%	0.302	24.4	4.5	24.0	21.0 to 27.0	14.0, 38.0
	Maximum aneurysm	152	2, 1%	<0.001	66.4	9.5	65.0	59.3 to 72.0	52.0, 108
	Maximum common iliac artery	94	60, 39%	<0.001	14.4	4.5	13	11.0 to 15.3	8.0, 31.0
Lengths, mm	CA to SMA	93	61, 40%	0.404	19.5	5.5	19.0	15.5 to 23.5	5.0, 34.0
	SMA to CrRA	94	60, 39%	0.014	12.4	6.9	11.0	7.0 to 16.0	0.0, 34.0
	CrRA to CaRA	93	61, 40%	<0.001	7.7	6.4	6.0	4.0 to 10.0	0.0, 39.0
	CaRA to BN	94	60, 39%	<0.001	8.4	8.8	6.5	0.0 to 13.0	0.0, 46.0
	BN to aortic bifurcation	94	60, 39%	0.209	129.6	19.5	127.5	115.0 to 143.3	84.0, 180.0
	Common iliac artery (mean)	93	61, 40%	0.422	62.9	14.4	63.0	52.3 to 74.0	33.5, 106.5
Angulation (°)	Maximum coronal neck	95	59, 38%	<0.001	25.8	17.2	23.0	12.0 to 37.0	0.0, 70.0
	Maximum sagittal neck	95	59, 38%	0.005	29.2	15.7	27.0	19.0 to 39.0	1.0, 85.0

IQR, inter-quartile range. Min, minimum. Max, maximum. Normality was tested using the Shapiro-Wilk test. Shading indicates the appropriate summary statistics based on the distribution of the data.

APP_2 Summary of demographic, clinical, preoperative morphological and graft-related factors(categorical variables)

Baseline characteristics	Available cohort, n	Missingness n, %	Characteristic present n, %
Gender, men	154	0, 0%	141, 92%
Smoking status, ex- or current	123	31, 20%	84, 68%
Ischaemic heart disease	127	27, 18%	64, 50%
Heart failure	126	28, 18%	9, 7%
Hypertension	127	27, 18%	84, 66%
Chronic renal insufficiency	126	28, 18%	10, 8%
Diabetes mellitus	127	27, 18%	15, 12%
ASA grade ≥ 3	117	37, 24%	84, 72%
Pre-operative CT scan			
Aortic neck calcification	95	59, 38%	8, 8%
Aortic neck thrombus	95	59, 38%	46, 48%
CIA calcification	93	60, 40%	40, 43%
CIA thrombus	93	60, 40%	33, 36%
Stent-graft details			
Design	154		
Bifurcated		0, 0%	112, 93%
AUI		0, 0%	5, 4%
Tube		0, 0%	4, 3%
Target vessel configuration			
≥ 1 TV stented	154	0, 0%	137, 89%
≥ 2 TV stented	154	0, 0%	40, 26%

Aortic neck calcification/thrombus was defined as present if it could be subjectively quantified as moderate or severe. CIA calcification and thrombus was treated in the same way and but the maximum score for the two vessels was recorded. AUI, aorto-uni-iliac. TV, target vessel.

APP_3 A summary of variables available from the 1st post-operative CT scan and database records (categorical variables)

Covariate	**Available cohort, n**	**Missingness n, %**	**Characteristic present n, %**
Target vessel loss	154	0, 0%	7, 5%
Any endoleak	154	0, 0%	24, 16%
Device kinking	154	0, 0%	5,3%
Component fracture	153	1, 1%	1, 1%
Iliac limb occlusion	152	2, 1%	9, 6%

Variables were assessed using the 1st postoperative CT and from entries in the respective databases.

APP_5 *A summary of variables available during follow-up (categorical variables) not from 1st CT scan.*

Covariate	**Available cohort**	**Missingness n, %**	**Characteristic present n, %**
Target vessel loss	154	0, 0%	16, 10%
Any endoleak	154	0, 0%	30, 20%
Kinking	154	0, 0%	19, 12%
Component fracture	154	0, 0%	20, 13%
Iliac limb occlusion	151	3, 2%	1, 1%

Variables were assessed using the 1st postoperative CT and from entries in the respective databases.

APP_4 *A summary of variables available from the 1st post-operative CT scan and database records (continuous variables)*

Covariate		n	Missingness n, %	Normality test, P value	Mean	SD	Median	IQR	Min, Max
Diameters, mm	Coeliac axis (CA)	150	4, 3%	<0.001	24.0	3.9	24.0	21.0 to 26.0	17.0, 42.0
	Superior mesenteric artery (SMA)	151	3, 2%	<0.001	23.1	3.8	23.0	20.0 to 25.0	16.0, 36.0
	Cranial renal arteries (CrRA)	151	3, 2%	<0.001	23.0	4.1	22.0	20.0 to 25.0	15.0, 40.0
	Caudal renal arteries (CaRA)	150	4, 3%	<0.001	22.8	4.4	22.0	20.0 to 25.0	14.0, 37.0
	Bottom aortic neck (BN)	151	3, 2%	<0.001	23.8	4.5	23.0	20.0 to 26.0	16.0, 37.0
	Maximum aneurysm	152	2, 1%	<0.001	68.6	10.9	67.0	60.0 to 74.8	51.0 to 112.0
	Maximum common iliac artery	150	4, 3%	<0.001	14.0	2.9	14.0	12.0 to 16.0	8.0, 24.0
Lengths, mm	CA to SMA	150	4, 3%	<0.001	19.4	6.6	18.0	15.0 to 23.0	5.0, 53.0
	SMA to CrRA	150	4, 3%	0.007	14.5	7.0	14.0	8.8 to 19.3	0.0, 34.0
	CrRA to CaRA	149	5, 3%	<0.001	5.7	6.5	5.0	0.0 to 8.0	0.0, 48.0
	CaRA to BN	150	4, 3%	<0.001	5.6	6.4	4.0	0.0 to 10.0	0.0, 25.0
	BN to aortic bifurcation	150	4, 3%	<0.001	124.1	18.6	121.0	111.0 to 134.3	86.0, 190.0
	Common iliac artery (mean)	150	4, 3%	0.059	56.8	13.1	56.2	47.5 to 64.6	29.5, 101.5
Angulation (°)	Maximum coronal neck	153	1, 1%	<0.001	16.9	11.4	15.0	9.0 to 22.0	0.0, 51.0
	Maximum sagittal neck	153	1, 1%	0.002	21.6	9.5	20.0	15.0 to 28.0	2.0, 44.0
Graft, mm	SMA to proximal stent-graft	154	0, 0%	<0.001	41.4	21.7	36.4	29.4 to 49.4	10.5, 140.6
	CIA to ipsilateral limb	127	27, 18%	<0.001	16.8	11.8	16.1	9.7 to 23.5	-46.8, 53.6
	CIA to contralateral limb	131	23, 15%	<0.001	17.8	14.0	17.5	9.0 to 25.2	-50.0, 73.8
	CA to distal bifurcated body	143	11, 7%	0.411	59.0	15.9	58.0	47.0 to 69.0	22.0, 106.0
	Ipsilateral limb diameter	138	16, 10%	<0.001	13.6	2.8	13.0	12.0 to 15.0	9.0, 23.0
	Contralateral limb diameter	139	15, 10%	<0.001	13.6	3.3	13.0	12.0 to 15.0	7.0, 28.0

IQR, inter-quartile range. Min, minimum. Max, maximum. Normality was tested using the Shapiro-Wilk test. Shading indicates the appropriate summary statistics based on the distribution of the data.

APP_6 *A summary of changes during follow-up (continuous variables)*

	Covariate	n	Missingness n, %	Normality test, P value	Mean	SD	Median	IQR	Min, Max
Diameters, mm	Coeliac axis (CA)	149	5, 3%	<0.001	1.4	2.4	1.0	0.0 to 2.0	-4.0, 14.0
	Superior mesenteric artery (SMA)	150	4, 3%	<0.001	2.2	2.2	2.0	1.0 to 3.0	-2.0, 11.0
	Cranial renal arteries (CrRA)	150	4, 3%	<0.001	2.7	2.6	2.0	1.0 to 4.0	-3.0, 12.0
	Caudal renal arteries (CaRA)	148	6, 4%	<0.001	3.2	2.6	3.0	1.0 to 5.0	-1.0, 12.0
	Bottom aortic neck (BN)	150	4, 3%	<0.001	3.1	3.2	3.0	1.0 to 5.0	-4.0, 15.0
	Maximum aneurysm	151	3, 2%	0.013	-8.6	10.9	-7.0	-17.0 to -1.0	-35.0, 30.0
	Maximum common iliac artery	148	6, 4%	<0.001	1.5	2.0	1.0	0.0 to 2.0	-3.0, 12.0
Lengths, mm	CA to SMA	149	5, 3%	<0.001	0.6	4.8	0.0	-2.0 to 2.0	-12.0, 24.0
	SMA to CrRA	149	5, 3%	<0.001	0.6	5.0	1.0	-2.0 to 3.0	-22.0 to 18.0
	CrRA to CaRA	147	7, 5%	<0.001	0.3	3.8	0.0	-1.0 to 2.0	-16.0, 11.0
	CaRA to BN	149	6, 3%	<0.001	7.5	13.1	4.0	0.0 to 11.0	-12.0, 95.0
	BN to aortic bifurcation	147	7, 5%	<0.001	-3.2	10.5	-2.0	-9.0 to 1.0	-53.0, 30.0
	Common iliac artery (mean)	145	9, 6%	<0.001	1.6	6.5	1.5	-0.5 to 3.0	-46.0. 27.0
Angulation (°)	Maximum coronal neck	152	2, 1%	0.011	-2.3	8.6	-2.0	-7.0 to 3.0	-26.0, 28.0
	Maximum sagittal neck	152	2, 1%	0.042	-4.0	7.4	-4.0	-9.0 to 0.0	-21.0, 25.0
Graft, mm	CA to distal bifurcated body length	140	14, 9%	<0.001	4.2	7.9	3.0	1.0 to 7.0	-30.0, 56.0
	Ipsilateral limb diameter	135	19, 12%	<0.001	2.6	4.6	2.0	1.0, 4.0	-0.4, 48.0
	Contralateral limb diameter	137	17, 11%	<0.001	2.2	2.4	2.0	1.0, 4.0	-8.0, 9.0

IQR, inter-quartile range. Min, minimum. Max, maximum. Normality was tested using the Shapiro-Wilk test. Shading indicates the appropriate summary statistics based on the distribution of the data. A negative value indicates a reduction in change. All distances are in millimetres.

APP_7 A summary of present and missing values for demographic and clinical covariates

	Proximal migration (≥ 4 mm)				
	No (n=121)		Yes (n=33)		P
Covariate	Present, n (%)	Missing, n (%)	Present, n (%)	Missing, n (%)	Value
Age (years)	119 (77%)	2 (1%)	32, (21%)	1, (1%)	0.518
Gender	121 (79%)	0 (0%)	33, (21%)	0, (0%)	***
Body mass index (kg/m^2)	78 (51%)	43 (28%)	17, (11%)	16, (10%)	0.125
Heart rate (b.p.m)	84 (55%)	37 (24%)	21, (14%)	12, (8%)	0.396
Systolic blood pressure (mmHg)	84 (55%)	37 (24%)	21, (14%)	12, (8%)	0.396
Serum haemoglobin (g/dl)	87 (56%)	34 (22%)	22, (14%)	11, (7%)	0.491
Smoking status	97 (63%)	24 (16%)	26, (17%)	7, (5%)	0.516
Ischaemic heart disease	101 (66%)	20 (13%)	26, (17%)	7, (5%)	0.346
Heart failure	100 (65%)	21 (14%)	26, (17%)	7, (5%)	0.388
Hypertension	101 (66%)	20 (13%)	26, (17%)	7, (5%)	0.346
Chronic renal insufficiency	100 (65%)	21 (14%)	26, (17%)	7, (5%)	0.388
Diabetes mellitus	101 (66%)	20 (13%)	26, (17%)	7, (5%)	0.346
ASA grade	93 (60%)	28 (18%)	24, (16%)	9, (6%)	0.388

P values were derived using Fisher's exact test. *** there were no missing values for this covariate.

APP_8 A summary of present and missing values for preoperative CT covariates

	Covariate	Proximal migration: No (n=121) Present, n (%)	No (n=121) Missing, n (%)	Yes (n=33) Present, n (%)	Yes (n=33) Missing, n (%)	P Value
Diameters, mm	Coeliac axis (CA)	81 (53%)	40 (26%)	13 (8%)	20 (13%)	0.004
	Superior mesenteric artery (SMA)	82 (53%)	39 (25%)	13 (8%)	20 (13%)	0.003
	Cranial renal artery (CrRA)	82 (53%)	39 (25%)	13 (8%)	20 (13%)	0.003
	Caudal renal artery (CaRA)	81 (53%)	40 (26%)	13 (8%)	20 (13%)	0.004
	Bottom aortic neck (BN)	82 (53%)	39 (25%)	13 (8%)	20 (13%)	0.003
	Maximum AAA (maxAAA)	120 (78%)	1 (1%)	32 (21%)	1 (1%)	***
	Maximum common iliac artery (maxCIA)	81 (53%)	40 (26%)	13 (8%)	20 (13%)	0.004
Lengths, mm	CA to SMA	80 (52%)	41 (27%)	13 (8%)	20 (13%)	0.024
	SMA to CrRA	81 (53%)	40 (26%)	13 (8%)	20 (13%)	0.016
	CrRA to CaRA	80 (52%)	41 (27%)	13 (8%)	20 (13%)	0.021
	CaRA to BN	81 (53%)	40 (26%)	13 (8%)	20 (13%)	0.016
	CaRA to aortic bifurcation	81 (53%)	40 (26%)	13 (8%)	20 (13%)	0.016
	Common Iliac Artery (mean)	80 (52%)	41 (27%)	13 (8%)	20 (13%)	0.005
Angulation, °	Maximum coronal neck	82 (53%)	39 (25%)	13 (8%)	20 (13%)	0.003
	Maximum sagittal neck	82 (53%)	39 (25%)	13 (8%)	20 (13%)	0.003
Categorical	Aortic neck calcification	82 (53%)	39 (25%)	13 (8%)	20 (13%)	0.003
	Aortic neck thrombus	80 (52%)	41 (27%)	13 (8%)	20 (13%)	0.005
	Visceral artery patency	82 (53%)	39 (25%)	13 (8%)	20 (13%)	0.003
	CIA calcification	80 (52%)	41 (27%)	13 (8%)	20 (13%)	0.005
	CIA thrombus	80 (52%)	41 (27%)	13 (8%)	20 (13%)	0.005

P values were derived using Fisher's exact test. *** there were no missing values for this covariate.

APP_9 A summary of present and missing values for graft design covariates

Covariate	Proximal migration: No (n=131) Present, n (%)	No (n=131) Missing, n (%)	Yes (n=33) Present, n (%)	Yes (n=33) Missing, n (%)	P value
Stent-graft diameter	67 (44%)	54 (35%)	16 (10%)	17 (11%)	0.306
Stent-graft length	57 (37%)	64 (42%)	11 (7%)	22 (14%)	0.112
Graft shape	121 (79%)	0 (0%)	33 (21%)	0 (0%)	***
Target vessel configuration	121 (79%)	0 (0%)	33 (21%)	0 (0%)	***

Stent-graft diameters and lengths refer to the proximal component. Graft shape; bifurcated, aorto-uni-iliac or tube. Target vessel configuration refers to details above the number and type of target vessels incorporated into the graft. P values were derived using Fisher's exact test. *** there were no missing values for this covariate.

APP_10 A summary of present and missing values for variables acquired from the 1st postoperative CT scan

		Proximal migration				
		No (n=121)		Yes (n=33)		
	Covariate	Present, n (%)	Missing, n (%)	Present, n (%)	Missing, n (%)	P value
Diameters, mm	Coeliac axis (CA)	117 (76%)	4 (3%)	33 (21%)	0 (0%)	0.377
	Superior mesenteric artery (SMA)	118 (77%)	3 (2%)	33 (21%)	0 (0%)	0.482
	Cranial renal artery (CrRA)	118 (77%)	3 (2%)	33(21%)	0 (0%)	0.482
	Caudal renal artery (CaRA)	117 (76%)	4 (3%)	33 (21%)	0 (0%)	0.263
	Bottom aortic neck (BN)	118 (77%)	3 (2%)	33 (21%)	0 (0%)	0.350
	Maximum AAA (maxAAA)	119 (77%)	2 (1%)	33(21%)	0 (0%)	0.905
	Ipsilateral CIA	115 (75%)	6 (4%)	31 (20%)	2 (1%)	0.543
	Contralateral CIA	108 (70%)	13 (8%)	30 (19%)	3 (2%)	0.538
Lengths, mm	CA to SMA	117 (76%)	4 (3%)	33 (21%)	0 (0%)	0.377
	SMA to CrRA	118 (77%)	3 (2%)	32 (21%)	1 (1%)	0.623
	CrRA to CaRA	117 (76%)	4 (3%)	32 (21%)	1 (1%)	0.709
	CaRA to BN	118 (77%)	3 (2%)	32 (21%)	1 (1%)	0.623
	CaRA to aortic bifurcation	118 (77%)	3 (2%)	32 (21%)	1 (1%)	0.623
	Ipsilateral CIA	106 (69%)	15 (10%)	30 (19%)	3 (2%)	0.432
	Contralateral CIA	107 (69%)	14 (9%)	30 (19%)	3 (2%)	0.484
Angulation, °	Maximum coronal neck	120 (78%)	1 (1%)	33 (21%)	0 (0%)	0.786
	Maximum sagittal neck	120 (78%)	1 (1%)	33 (21%)	0 (0%)	0.786
Graft, mm	SMA to proximal stent-graft	121 (79%)	0 (0%)	33 (21%)	0 (0%)	***
	CIA to ipsilateral iliac limb	106 (69%)	15 (10%)	30 (19%)	3 (2%)	0.432
	CIA to contralateral iliac limb	107 (69%)	14 (9%)	30 (19%)	3 (2%)	0.484
	CA to distal bifurcated component	111 (72%)	10 (6%)	32 (21%)	1 (1%)	0.271
	Ipsilateral limb diameter	108 (70%)	13 (8%)	30 (19%)	3 (2%)	0.538
	Contralateral limb diameter	108 (70%)	13 (8%)	31 (20%)	2 (1%)	0.554
Categorical	Target vessel patency	119 (77%)	2 (1%)	33 (21%)	0 (0%)	0.616
	Endoleak	118 (77%)	3 (2%)	33 (21%)	0 (0%)	0.482
	Kinking	120 (78%)	1 (1%)	33 (21%)	0 (0%)	0.786
	Component fracture	120 (78%)	1 (1%)	33 (21%)	0 (0%)	0.786
	Iliac limb occlusion	119 (77%)	2 (1%)	33 (21%)	0 (0%)	0.616

P values were derived using Fisher's exact test. *** there were no missing values for this covariate.

APP_11 A summary of present and missing values for variables ascertained from changes during follow-up

		Proximal migration				
		No (n=121)		Yes (n=33)		
	Covariate	**Present, n (%)**	**Missing, n (%)**	**Present, n (%)**	**Missing, n (%)**	**P value**
Diameters, mm	Coeliac axis (CA)	116 (96%)	5 (4%)	33 (100%)	0 (0%)	0.29
	Superior mesenteric artery (SMA)	117 (97%)	4 (3%)	33 (100%)	0 (0%)	0.38
	Cranial renal artery (CrRA)	115 (95%)	6 (5%)	33 (100%)	0 (0%)	0.23
	Caudal renal artery (CaRA)	115 (95%)	6 (5%)	33 (100%)	0 (0%)	0.23
	Bottom aortic neck (BN)	121 (100%)	0 (0%)	33 (100%)	0 (0%)	***
	Maximum AAA (maxAAA)	121 (100%)	0 (0%)	33 (100%)	0 (0%)	***
	Ipsilateral CIA	112 (93%)	9 (7%)	31 (94%)	2 (6%)	0.57
	Contralateral CIA	105 (87%)	16 (13%)	30 (91%)	3 (9%)	0.38
Lengths, mm	CA to SMA	116 (96%)	5 (4%)	33 (100%)	0 (0%)	0.29
	SMA to CrRA	117 (97%)	4 (3%)	32 (97%)	1 (3%)	0.71
	CrRA to CaRA	115 (95%)	6 (5%)	33 (100%)	0 (0%)	0.23
	CaRA to BN	117 (97%)	4 (3%)	32 (97%)	1 (3%)	0.71
	CaRA to aortic bifurcation	116 (96%)	5 (4%)	31 (94%)	2 (6%)	0.47
	Ipsilateral CIA	103 (85%)	18 (15%)	27 (82%)	6 (18%)	0.41
	Contralateral CIA	104 (86%)	17 (14%)	27 (18%)	6 (18%)	0.36
Angulation, °	Maximum coronal neck	119 (98%)	2 (2%)	33 (100%)	0 (0%)	0.62
	Maximum sagittal neck	119 (98%)	2 (2%)	33 (100%)	0 (0%)	0.62
Graft	SMA to proximal stent-graft	121 (100%)	0 (0%)	33 (100%)	0 (0%)	***
	CIA to ipsilateral iliac limb	102 (84%)	19 (16%)	27 (82%)	6 (18%)	0.46
	CIA to contralateral iliac limb	103 (85%)	18 (15%)	27 (82%)	6 (18%)	0.41
	CA to distal bifurcated body	108 (89%)	13 (11%)	32 (97%)	1 (3%)	0.15
	Ipsilateral limb diameter	105 (87%)	16 (13%)	30 (91%)	3 (9%)	0.38
	Contralateral limb diameter	106 (88%)	15 (12%)	31 (94%)	2 (6%)	0.25
Categorical	Target vessel patency	119 (77%)	2 (1%)	33 (21%)	0 (0%)	0.616
	Endoleak	119 (77%)	2 (1%)	33 (21%)	0 (0%)	0.616
	Kinking	119 (77%)	2 (1%)	33 (21%)	0 (0%)	0.616
	Component fracture	120 (78%)	1 (1%)	33 (21%)	0 (0%)	0.786
	Iliac limb occlusion	118 (77%)	3 (2%)	33 (21%)	0 (0%)	0.482

P values were derived using Fisher's exact test. *** there were no missing values for this covariate.

APP_12 Univariate analysis of demographic and clinical factors associated with proximal (≥ 4 mm) stent-graft migration

	No Proximal Migration (n=121)							Proximal Migration (n=33)							P
	n (%)	Normality test P value	Mean	SD	Median	IQR	Min, Max	n (%)	Normality test P value	Mean	SD	Median	IQR	Min, Max	value
Age (years)		0.01	74.2	6.8	75.0	69.0 - 79.0	54.0, 87.0		0.550	72.7	6.4	73.0	68.3 - 76.8	59.0, 86.0	0.21
Body mass index (kg/m^2)		0.03	27.7	4.3	27.0	25.0-30.6	19.1, 39.0		0.001	28.3	5.4	26.5	25.3 - 29.9	22.6, 45.4	0.87
Heart rate (bpm)		<0.01	72	13	**70**	**64-82**	49, 100		0.015	68	16	**70**	**57 - 74**	48, 112	**0.07**
Syst. blood pressure (mmHg)		0.11	141	23	140	125-152	92, 200		0.028	146	27	140	128 - 165	113, 208	0.80
Serum haemoglobin (g/dl)		<0.01	13.7	1.6	**13.8**	**13.0-14.8**	9.5, 16.6		0.169	14.3	1.6	**14.4**	**13.3 - 15.8**	11.0, 16.5	**0.09**
Gender, men*	110 (91%)							31 (94%)							0.44
Smoking status, ex-/current*	**63 (65%)**							**21 (81%)**							**0.09**
Ischaemic heart disease*	51 (51%)							13 (50%)							0.57
Heart failure*	8 (8%)							1 (4%)							0.41
Hypertension*	68 (67%)							16 (62%)							0.37
Chronic renal insufficiency*	6 (6%)							4 (15%)							0.12
Diabetes mellitus*	12 (12%)							3 (12%)							0.63
ASA grade ≥ 3*	64 (69%)							20 (83%)							0.12

Normality was assessed using the Shapiro-Wilk test. SD, standard deviation; IQR, inter-quartile range; MIN, minimum; MAX, maximum. Bold text in the P value column indicates those parameters that achieved values less 0.1. P values for categorical variables (indicated by an asterisk*) are expressed using the Fisher Exact test. Parameters shaded in grey refer to the appropriate descriptive statistic when considering the distribution of the data.

APP_13 Univariate analysis of pre-operative CT morphological factors for association with proximal (≥ 4 mm) stent-graft migration

		No Proximal Migration (n=121)							Proximal Migration (n=33)							
		n (%)	NT P value	Mean	SD	Median	IQR	Min, Max	n (%)	NT P value	Mean	SD	Median	IQR	Min, Max	P value
DIAMETERS (MM)	Coeliac axis (CA)		0.14	25	3	25	24 - 27	19, 34		0.095	26	2	26	25 - 28	23, 32	0.22
	Sup. mesenteric (SMA)		0.13	24	3	24	22 - 26	18, 33		0.785	24	3	24	23 - 27	19, 29	0.98
	Cranial renal artery (CrRA)		0.05	23	4	23	21 - 25	16, 33		0.309	24	3	25	21 - 27	20, 31	0.30
	Caudal renal artery (CaRA)		0.03	24	4	23	21 - 26	14, 38		0.293	24	5	24	20 - 27	18, 33	0.90
	Bottom aortic neck (BN)		0.23	24	4	24	21 - 27	14, 38		0.552	26	5	26	22 - 31	19, 33	**0.09**
	AAA (MAX)		<0.01	66	9	63	59 - 73	52, 90		0.103	68	11	69	60 - 70	56, 108	0.27
	CIA (MAX)		<0.01	14	4	14	11 - 16	8, 31		0.001	14	5	12	11 - 15	10, 28	0.25
LENGTHS (MM)	CA to SMA		0.55	19	6	19	15 - 23	5, 32		0.072	20	5	19	16 - 24	14, 34	0.62
	SMA to CrRA		<0.01	13	7	11	8 - 16	2, 34		0.529	11	6	11	7 - 17	0, 20	0.75
	CrRA to CaRA		<0.01	8	7	6	4 - 10	0, 39		0.823	7	5	8	4 - 11	0, 18	0.81
	CaRA to BN		<0.01	9	9	7	0 - 13	0, 46		0.054	7	7	5	0 - 13	0, 20	0.69
	CaRA to aortic bifurcation		0.57	130	19	128	115 - 144	84, 180		0.115	130	21	125	113 - 147	108, 170	0.88
	Mean CIA		0.55	63	15	63	52 - 74	34, 107		0.379	63	12	63	55 - 73	39, 78	0.98
ANGLE (°)	**Coronal neck (Max)**		<0.01	27	18	25	13-38	0, 70		0.452	17	9	17	9 - 26	2, 30	**0.06**
	Sagittal neck (Max)		<0.01	29	16	27	19-40	1, 85		0.160	28	14	23	18 - 39	11, 56	0.73
VESSEL QUALITY	Aortic neck calcification*	7 (9%)							1 (8%)							0.70
	Aortic neck thrombus*	39 (48%)							7 (54%)							0.45
	Maximum CIA thrombus*	**33 (28%)**							**5 (15%)**							**0.09**
	Maximum CIA calc.	42 (35%)							8 (25%)							0.20

Normality was assessed using the Shapiro-Wilk test. SD, standard deviation; IQR, inter-quartile range; MIN, minimum; MAX, maximum. Bold/underlined text indicates those parameters that achieved values less 0.1. P values for categorical variables (indicated by an asterisk*) are expressed using the Fisher Exact test. Parameters shaded in grey refer to the appropriate descriptive statistic when considering the distribution of the data.

APP-14 Univariate analysis of the influence of graft-related features on proximal (≥ 4 mm) stent-graft migration

	No Proximal Migration (n=131)							Proximal Migration (n=33)							P value
	n (%)	Normality test P value	Mean	SD	Median	IQR	Min, Max	n (%)	Normality test P value	Mean	SD	Median	IQR	Min, Max	
Stent-graft diameter		0.01	29	4	28	26 - 32	20, 38		0.61	29	5	28	27 - 32	20, 40	0.84
Stent-graft length		<0.01	122	21	124	109 - 136	88, 183		<0.01	124	29	109	106 - 139	94, 181	0.80
Graft shape															
Bifurcated	112 (93%)							30 (91%)							
AUI	5 (4%)							1 (3%)							0.74
Tube	4 (3%)							2 (6%)							
Target vessel configuration															
≥ 1 TV stented*	**105 (87%)**							**32 (97%)**							**0.08**
≥ 2 TV stented*	**35 (29%)**							**5 (15%)**							**0.08**

Normality was assessed using the Shapiro-Wilk test. SD, standard deviation; IQR, inter-quartile range; Min, minimum; Max, maximum. Bold/underlined text indicates those parameters that achieved values less 0.1. P values for categorical variables (indicated by an asterisk*) are expressed using the Fisher Exact test all other categorical variables have been assessed using a Chi-squared test. Parameters shaded in grey refer to the appropriate descriptive statistic when considering the distribution of the data.

APP_15 Univariate analysis of the influence of follow-up complications on proximal (≥ 4 mm) stent-graft migration.

	1st post-operative CT Scan			Any subsequent CT scan		
	No Proximal Migration (n=121)	**Proximal Migration (n=33)**	**P value**	**No Proximal Migration (n=121)**	**Proximal Migration (n=33)**	**P value**
Target vessel patency*	1 (1%)	2 (6%)	0.12	6 (5%)	1 (3%)	0.54
Endoleak						
1-P	9 (7%)	2 (6%)		1 (1%)	1 (3%)	
1-D	0 (0%)	0 (0%)	0.78	0 (0%)	0 (0%)	0.39
II	7 (6%)	3 (9%)		17 (14%)	2 (6%)	
III	0 (0%)	0 (0%)		2 (2%)	0 (0%)	
Limb occlusion*	7 (9%)	0 (0%)	0.34	1 (1%)	3 (9%)	0.03
Kinking*				1 (1%)	0 (0%)	0.78
Component fracture*				50 (46%)	17 (53%)	0.50
Component separation ≥4 mm*				12 (11%)	6 (19%)	0.26
Component separation ≥10 mm*				2 (2%)	1 (6%)	0.40

Bold text in the P value column indicates those parameters which were less than 0.1. P values for categorical variables (indicated by an asterisk*) are expressed using the Fisher Exact test, all other categorical variables have been assessed using a Chi-squared test.

APP_16 Univariate analysis of the influence of 1st post-operative CT factors on proximal (≥ 4 mm) stent-graft migration

	Covariate	No Proximal Migration (n=121)						Proximal Migration (n=33)						P value
		Normality test, P value	Mean	SD	Median	IQR	Min, Max	Normality test, P value	Mean	SD	Median	IQR	Min, Max	
DIAMETERS (MM)	Coeliac axis (CA)	<0.001	24	3	23	21 - 26	18, 35	<0.001	25	5	24	22 - 27	17, 42	0.23
	Superior mesenteric artery (SMA)	<0.001	23	4	23	20 - 25	16, 36	0.001	24	4	23	20 - 25	17, 36	0.40
	Cranial renal artery (CrRA)	<0.001	23	4	22	20 - 25	15, 40	<0.001	24	5	23	21 - 27	18, 37	0.20
	Caudal renal artery (CaRA)	<0.001	22	4	22	20 - 25	14, 34	0.001	24	5	23	20 - 29	18, 37	0.19
	Bottom aortic neck (BN)	<0.001	23	4	23	20 - 26	16, 35	0.13	25	5	24	22 - 30	18, 37	**0.07**
	AAA (MAX)	<0.001	68	10	66	60 - 74	51, 98	<0.001	71	12	70	61 - 77	55, 112	0.19
	Ipsilateral CIA	<0.001	13	3	13	11 - 14	7, 24	0.03	13	3	13	11 - 15	9, 19	0.89
	Contralateral CIA	<0.001	13	3	13	11 - 15	8, 22	0.04	12	3	12	11 - 14	8, 20	**0.09**
LENGTHS (MM)	CA to SMA	<0.001	19	7	18	15 - 22	5, 53	0.04	21	7	20	16 - 25	10, 40	0.17
	SMA to CrRA	<0.001	14	7	13	9 - 20	0, 34	0.63	14	7	15	8 - 19	0, 28	0.93
	CrRA to CaRA	<0.001	5	7	5	0 - 7	0, 48	<0.001	6	6	5	2 - 10	0, 21	0.33
	CaRA to BN	<0.001	6	7	5	0 - 11	0, 25	<0.001	3	5	0	0 - 7	0, 17	**0.02**
	CaRA to aortic bifurcation	<0.001	123	19	120	110 - 134	86, 190	<0.001	129	18	124	117 - 136	108, 184	**0.09**
	Ipsilateral CIA	<0.001	56	13	56	48 - 62	31, 129	0.29	56	17	54	46 - 64	29, 103	0.65
	Contralateral CIA	0.84	57	15	57	48 - 67	24, 98	0.58	58	16	56	47 - 70	29, 100	0.69
ANGLE (°)	Coronal neck (MAX)	<0.01	18	12	15	9 - 23	0, 51	<0.001	14	9	11	8 - 19	1, 45	0.11
	Sagittal neck (MAX)	<0.01	22	10	20	15 - 28	2, 44	0.38	22	9	20	16 - 29	6, 40	0.94
GRAFT (MM)	SMA to proximal stent-graft	<0.01	41	20	36	29 - 50	11, 130	<0.001	44	27	37	33 - 41	11.7, 141	0.51
	CIA to ipsilateral iliac limb	<0.01	16	12	15	9 - 22	-47, 54	0.75	20	9	20	16 - 27	-1, 36	**0.02**
	CIA to contralateral iliac limb	<0.01	17	13	17	7 - 24	-50, 46	<0.001	22	15	19	11 - 27	0, 74	0.16
	CA to distal bifurcated component	0.56	59	16	58	46 - 71	22, 106	0.28	60	16	60	51 - 69	24, 101	0.74
	Ipsilateral limb diameter (stent)	<0.01	14	3	13	12 - 14	9, 23	0.34	14	6	13	12 - 15	9, 20	0.66
	Contralateral limb diameter (stent)	<0.01	14	3	13	12 - 15	8, 28	<0.001	13	3	13	11 - 13	7, 20	**0.02**

Normality was assessed using the Shapiro-Wilk test. SD, standard deviation; IQR, inter-quartile range; MIN, minimum; MAX, maximum. Bold text in the P value column indicates those parameters that achieved values less 0.1. Parameters shaded in grey refer to the appropriate descriptive statistic when considering the distribution of the data.

APP_17 Univariate analysis of the influence of changes in post-operative CT morphological factors on proximal (≥ 4 mm) stent-graft migration

		No Proximal Migration (n=121)						Proximal Migration (n=33)						P value
		Normality test, P value	Mean	SD	Median	IQR	Min, Max	Normality test, P value	Mean	SD	Median	IQR	Min, Max	
DIAMETERS (MM)	Coeliac axis (CA)	<0.001	1.2	2.3	1.0	0.0 - 2.0	-3.0, 14.0	0.58	2.0	2.6	2.0	0.5 - 4.0	-4.0, 9.0	**0.03**
	Superior mesenteric artery (SMA)	<0.001	2.1	2.1	2.0	1.0 - 3.0	-2.0, 11.0	0.05	2.7	2.6	2.0	1.0 - 4.0	-2.0, 9.0	0.16
	Cranial renal artery (CrRA)	<0.001	2.5	2.4	2.0	1.0 - 4.0	-2.0, 12.0	0.88	3.6	3.2	4.0	1.0 - 6.0	-3.0, 11.0	**0.06**
	Caudal renal artery (CaRA)	<0.001	2.9	2.4	2.0	1.0 - 4.0	-1.0, 12.0	0.35	4.1	3.1	4.0	2.0 - 7.0	-1.0, 11.0	**0.03**
	Bottom aortic neck (BN)	<0.001	2.9	3.0	3.0	1.0 - 5.0	-4.0, 12.0	0.02	3.6	4.0	3.0	1.0 - 5.0	-3.0, 15.0	0.42
	AAA (MAX)	<0.001	7.7	10.0	7.0	1.8 - 15.0	-30.0, 35.0	0.33	11.8	13.4	13.0	1.0 - 22.5	-13.0, 35.0	0.11
	Ipsilateral CIA	<0.001	0.5	1.9	0.0	0.0 - 1.0	-5.0, 6.0	0.22	0.3	1.9	0.0	-1.0 - 2.0	-3.0, 5.0	0.58
	Contralateral CIA	<0.001	0.6	2.5	0.0	-1.0 - 2.0	-7.0, 12.0	0.02	0.9	2.2	1.0	-1.0 - 2.0	-3.0, 8.0	0.37
LENGTHS (MM)	CA to SMA	<0.001	0.8	5.0	0.0	-1.0 - 2.0	-12.0, 24.0	0.75	-0.1	4.4	0.0	-3.0 - 2.0	-11.0, 10.0	0.71
	SMA to CrRA	<0.001	0.1	4.8	1	-2.0 - 2.0	-22, 18	<0.01	2.4	5	2	-0.8 - 4.0	-7, 17	**0.03**
	CrRA to CaRA	<0.001	0.1	3.9	0	-2.0 - 2.0	-16, 11	<0.01	1	3.5	1	0.0 - 2.8	-10, 6	**0.08**
	CaRA to BN	<0.001	7.7	14	4	0.0 - 11.0	-12, 95	<0.01	6.5	9.6	2.5	0.0 - 11.8	-7, 32	0.72
	CaRA to aortic bifurcation	<0.001	-2.1	8.9	-2	-8.0 - 1.8	-28, 30	<0.01	-7.1	14.7	-6	-13.0 - 1.0	-53, 30	**0.07**
	Ipsilateral CIA	<0.001	2.1	5.6	2	-1.0 - 4.0	-18, 31	0.72	1.3	3.7	1	-1.0 - 3.0	-5, 10	0.50
	Contralateral CIA	<0.001	1.8	8.5	1	-1.0 - 4.0	-46, 41	<0.01	1.3	4.9	1	0.0 - 2.0	-14, 10	0.84
ANGLE (°)	Coronal neck (MAX)	0.001	2.4	6.7	2	-2.0 - 5.0	-15, 28	<0.01	2.5	7.2	1	-1.0 - 6.0	-13, 28	0.91
	Sagittal neck (MAX)	<0.001	-0.2	6.3	0	-3.0 - 2.0	-20, 18	<0.01	0.5	9.7	-2	-5.0 - 4.0	-15, 40	0.61

APP_18 Multivariate Cox proportional hazard model using the R package, beginning of interval (variables P<0.1 included)

ENTER METHOD (R) P<0.1	Univariate 95%CI				Multivariate 95%CI			
Beginning of interval	HR	Lower	Upper	P Value	HR	Lower	Upper	P Value
Heart rate (b.p.m)	0.97	0.94	1.01	0.16	0.84	0.00	1558.13	0.96
Serum haemoglobin (g/dl)	1.18	0.87	1.59	0.29	2.44	0.00	4.01E+22	0.97
Ex- or current smoker	2.68	0.92	7.82	0.07	348.16	0.00	7.04E+44	0.91
≥ 2 TV stented	0.60	0.23	1.58	0.30	849.90	0.00	7.53E+63	0.92
Ipsilateral CIA deployment distance, mm	1.02	0.99	1.05	0.17	1.07	0.02	53.73	0.97
Contralateral limb diameter, mm	0.85	0.75	0.97	0.02	0.46	0.00	5.67E+15	0.97
Preop bottom aortic neck diameter, mm	1.13	0.99	1.29	0.08	0.85	0.00	8.12E+10	0.99
Preop (max) coronal neck angulation, °	0.97	0.93	1.01	0.10	1.00	0.04	23.03	1.00
Preop (max) CIA thrombus	2.67	0.84	8.47	0.10	0.00	0.00	4.85E+59	0.94
1st postop bottom neck diameter, mm	1.08	1.01	1.16	0.03	1.46	0.00	9.43E+10	0.98
1st postop contralateral CIA diameter, mm	0.97	0.93	1.01	0.10	0.16	0.00	8.80E+18	0.94
1st postop aortic neck length, mm	0.91	0.84	0.97	0.01	0.45	0.00	4508.08	0.87
1st postop caudal renal artery to bifurcation length, mm	1.01	1.00	1.03	0.11	1.16	0.02	86.31	0.95
Postop diameter change - coeliac axis, mm	1.08	0.97	1.20	0.18	2.13	0.00	8.05E+15	0.97
Postop diameter change - cranial renal artery, mm	1.12	0.99	1.27	0.08	2.52	0.00	1.48E+13	0.95
Postop diameter change - caudal renal artery, mm	1.11	0.98	1.25	0.09	0.66	0.00	2.63E+16	0.98
Postop length change - SMA to cranial RA, mm	1.07	1.01	1.14	0.03	4.28	0.00	9.88E+09	0.89
Postop length change - cranial RA to caudal RA, mm	1.05	0.95	1.15	0.04	5.22	0.00	9.43E+08	0.86
Postop length change - caudal RA to aortic bif, mm	0.96	0.94	0.99	0.01	1.02	0.00	1433.28	1.00
Graft kinking	1.70	0.65	4.42	0.28	67563.62	0.00	2.22E+275	0.97

Multivariate analysis was conducted using the statistical programme R. CI, confidence interval. HR, hazard ratio.

APP_19 Multivariate Cox proportional hazard model using the R package, midpoint of interval (variables P<0.1 included)

ENTER METHOD P<0.1	Univariate 95%CI				Multivariate 95%CI			
Midpoint of interval	HR	Lower	Upper	P Value	HR	Lower	Upper	P Value
Heart rate (b.p.m)	0.98	0.94	1.01	0.21	0.96	0.05	17.43	0.98
Serum haemoglobin (g/dl)	1.14	0.85	1.53	0.39	2.84	0.00	3.11E+05	0.86
Ex- or current smoker	3.04	1.04	8.88	0.04	41.62	0.00	1.74E+19	0.86
≥ 2 TV stented	0.74	0.28	1.94	0.54	8053.81	0.00	1.15E+31	0.78
Ipsilateral CIA deployment distance, mm	1.02	0.99	1.05	0.29	1.01	0.21	4.85	0.99
Contralateral limb diameter, mm	0.85	0.75	0.97	0.02	0.85	0.00	3.51E+05	0.98
Preop bottom aortic neck diameter, mm	1.15	1.00	1.32	0.05	0.42	0.00	4.22E+03	0.86
Preop (max) coronal neck angulation, °	0.97	0.92	1.01	0.12	0.95	0.17	5.35	0.96
Preop (max) CIA thrombus	3.04	0.93	9.93	0.07	0.03	0.00	4.78E+16	0.87
1st postop bottom neck diameter, mm	1.09	1.01	1.17	0.02	1.30	0.00	1.07E+04	0.95
1st postop contralateral CIA diameter, mm	0.91	0.79	1.04	0.17	0.41	0.00	1.46E+06	0.91
1st postop aortic neck length, mm	0.90	0.83	0.97	0.00	0.52	0.02	11.82	0.68
1st postop caudal renal artery to bifurcation length, mm	1.02	1.00	1.03	0.09	1.01	0.26	3.93	0.99
Postop diameter change - coeliac axis, mm	1.08	0.97	1.21	0.14	1.30	0.00	7.51E+05	0.97
Postop diameter change - cranial renal artery, mm	1.12	0.98	1.27	0.09	2.15	0.00	1.72E+05	0.89
Postop diameter change - caudal renal artery, mm	1.10	0.97	1.24	0.15	0.58	0.00	4.31E+06	0.95
Postop length change - SMA to cranial RA, mm	1.06	1.00	1.13	0.07	3.85	0.01	1.31E+03	0.65
Postop length change - cranial RA to caudal RA, mm	1.04	0.94	1.14	0.47	3.64	0.00	2.13E+04	0.77
Postop length change - caudal RA to aortic bif, mm	0.96	0.94	0.99	0.01	0.99	0.13	7.52	0.99
Graft kinking	1.84	0.71	4.79	0.21	3.53	0.00	1.71E+147	0.99

Multivariate analysis was conducted using the statistical programme R. CI, confidence interval. HR, hazard ratio.

APP_20 Multivariate Cox proportional hazard model using the R package, end of interval (variables P<0.1 included)

ENTER METHOD (R) P<0.1	Univariate 95%CI				Multivariate 95%CI			
Endpoint of interval	HR	Lower	Upper	P Value	HR	Lower	Upper	P Value
Heart rate (b.p.m)	0.98	0.94	1.02	0.28	0.98	0.00	3.32E+04	1.00
Serum haemoglobin (g/dl)	1.06	0.79	1.43	0.69	2.77	0.00	5.06E+36	0.98
Ex- or current smoker	3.43	1.16	10.11	0.03	19.67	0.00	1.75E+70	0.97
≥ 2 TV stented	0.87	0.33	2.30	0.78	1.28E+04	0.00	1.21E+150	0.96
Ipsilateral CIA deployment distance, mm	1.01	0.98	1.04	0.48	0.95	0.00	6.45E+03	0.99
Contralateral limb diameter, mm	0.84	0.73	0.95	0.01	0.65	0.00	4.64E+12	0.98
Preop bottom aortic neck diameter, mm	1.18	1.01	1.38	0.03	0.29	0.00	1.97E+11	0.93
Preop (max) coronal neck angulation, °	0.97	0.93	1.01	0.17	0.94	0.01	8.55E+01	0.98
Preop (max) CIA thrombus	3.49	1.01	12.09	0.05	0.04	0.00	3.66E+109	0.98
1st bottom neck diameter, mm	1.09	1.01	1.17	0.02	1.18	0.00	2.03E+11	0.99
1st contralateral CIA diameter, mm	0.91	0.80	1.05	0.20	1.20	0.00	6.10E+25	1.00
1st aortic neck length, mm	0.89	0.83	0.96	0.00	0.49	0.00	8.46E+02	0.85
1st caudal renal artery to bifurcation length, mm	1.01	1.00	1.03	0.12	0.97	0.01	8.81E+01	0.99
Diameter change - coeliac axis, mm	1.08	0.97	1.20	0.17	0.61	0.00	1.58E+31	0.99
Diameter change - cranial renal artery, mm	1.11	0.97	1.26	0.11	4.65	0.00	8.43E+16	0.94
Diameter change - caudal renal artery, mm	1.07	0.94	1.22	0.29	0.37	0.00	3.27E+28	0.98
Length change - SMA to cranial RA, mm	1.05	0.98	1.12	0.14	4.16	0.00	3.79E+10	0.90
Length change - cranial RA to caudal RA, mm	1.04	0.94	1.14	0.47	3.43	0.00	1.23E+11	0.92
Length change - caudal RA to aortic bif, mm	0.97	0.75	1.25	0.01	1.02	0.00	2.99E+02	1.00
Graft kinking	1.79	0.69	4.65	0.23	0.00	0.00	NA	0.99

Multivariate analysis was conducted using the statistical programme R. CI, confidence interval. HR, hazard ratio.

APP_21 Multivariate Cox proportional hazard model using the SPSS package, beginning of interval (variables P<0.1 included)

MULIVARIATE (SPSS)	ENTER				FORWARD				BACKWARD			
		95%CI				95%CI				95%CI		
Beginning of the interval P<0.1	HR	Lower	Upper	P Value	HR	Lower	Upper	P Value	HR	Lower	Upper	P Value
Heart rate (b.p.m)	0.87	0.06	11.97	0.92					0.87	0.06	11.97	0.92
Serum haemoglobin (g/dl)	1.91	0.00	3.08E+07	0.94					1.91	0.00	3.08E+07	0.94
Ex- or current smoker	0.02	0.00	3.00E+13	0.83					0.02	0.00	3.00E+13	0.83
≥ 2 TV stented	0.01	0.00	3.50E+19	0.86					0.01	0.00	3.50E+19	0.86
Ipsilateral CIA deployment distance, mm	1.04	0.27	4.07	0.95					1.04	0.27	4.07	0.95
Contralateral limb diameter, mm	0.56	0.00	1.75E+05	0.93					0.56	0.00	1.75E+05	0.93
Preop bottom aortic neck diameter, mm	0.87	0.00	4.97E+03	0.98					0.87	0.00	4.97E+03	0.98
Preop (max) coronal neck angulation, °	1.00	0.32	3.09	1.00					1.00	0.32	3.09	1.00
Preop (max) CIA thrombus	30.86	0.00	8.38E+22	0.89					30.9	0.00	8.38E+22	0.89
1st bottom neck diameter, mm	1.36	0.00	9.31E+03	0.95					1.36	0.00	9.31E+03	0.95
1st contralateral CIA diameter, mm	0.29	0.00	7.10E+05	0.87					0.29	0.00	7.10E+05	0.87
1st aortic neck length, mm	0.57	0.03	12.47	0.72					0.57	0.03	12.47	0.72
1st caudal renal artery to bifurcation length, mm	1.12	0.24	5.15	0.89					1.12	0.24	5.15	0.89
Diameter change - coeliac axis, mm	1.81	0.00	5.20E+05	0.93					1.81	0.00	5.20E+05	0.93
Diameter change - cranial renal artery, mm	1.93	0.00	4.77E+04	0.90					1.93	0.00	4.77E+04	0.90
Diameter change - caudal renal artery, mm	0.80	0.00	1.91E+05	0.97					0.8	0.00	1.91E+05	0.97
Length change - SMA to cranial RA, mm	2.72	0.00	4.22E+03	0.79					2.72	0.00	4.22E+03	0.79
Length change - cranial RA to caudal RA, mm	3.08	0.00	1.95E+03	0.73					3.08	0.00	1.95E+03	0.73
Length change - caudal RA to aortic bif, mm	1.03	0.10	11.20	0.98					1.03	0.10	11.20	0.98
Graft kinking	0.00	0.00	5.68E+113	0.96					0.00	0.00	5.68E+113	0.96

Multivariate analysis was conducted using the statistical programme SPSS. CI, confidence interval. HR, hazard ratio.

APP_22 Multivariate Cox proportional hazard model using the SPSS package, midpoint of interval (variables P<0.1 included)

MULIVARIATE (SPSS)	ENTER 95%CI				FORWARD 95%CI				BACKWARD 95%CI			
Midpoint of the interval P<0.1	HR	Lower	Upper	P Value	HR	Lower	Upper	P Value	HR	Lower	Upper	P Value
Heart rate (b.p.m)	0.96	0.27	3.39	0.95					0.96	0.27	3.39	0.95
Serum haemoglobin (g/dl)	2.18	0.01	4.29E+02	0.77					2.18	0.01	4.29E+02	0.77
Ex- or current smoker	0.06	0.00	3.29E+06	0.76					0.06	0.00	3.29E+06	0.76
≥ 2 TV stented	0.00	0.00	2.72E+09	0.66					0.00	0.00	2.72E+09	0.66
Ipsilateral CIA deployment distance, mm	1.01	0.50	2.03	0.98					1.01	0.50	2.03	0.98
Contralateral limb diameter, mm	0.86	0.00	3.38E+02	0.96					0.86	0.00	3.38E+02	0.96
Preop bottom aortic neck diameter, mm	0.54	0.01	3.81E+01	0.78					0.54	0.01	3.81E+01	0.78
Preop (max) coronal neck angulation, °	0.95	0.45	2.02	0.90					0.95	0.45	2.02	0.90
Preop (max) CIA thrombus	11.47	0.00	1.42E+09	0.80					11.47	0.00	1.42E+09	0.80
1st bottom neck diameter, mm	1.17	0.02	7.11E+01	0.94					1.17	0.02	7.11E+01	0.94
1st contralateral CIA diameter, mm	0.58	0.00	5.40E+02	0.88					0.58	0.00	5.40E+02	0.88
1st aortic neck length, mm	0.63	0.15	2.63	0.53					0.63	0.15	2.63	0.53
1st caudal renal artery to bifurcation length, mm	1.01	0.54	1.92	0.97					1.01	0.54	1.92	0.97
Diameter change - coeliac axis, mm	1.28	0.00	3.97E+02	0.93					1.28	0.00	3.97E+02	0.93
Diameter change - cranial renal artery, mm	1.70	0.01	2.31E+02	0.83					1.70	0.01	2.31E+02	0.83
Diameter change - caudal renal artery, mm	0.70	0.00	7.13E+02	0.92					0.70	0.00	7.13E+02	0.92
Length change - SMA to cranial RA, mm	2.62	0.21	3.29E+01	0.46					2.62	0.21	3.29E+01	0.46
Length change - cranial RA to caudal RA, mm	2.61	0.06	1.10E+02	0.62					2.61	0.06	1.10E+02	0.62
Length change - caudal RA to aortic bif, mm	1.00	0.40	2.51	1.00					1.00	0.40	2.51	1.00
Graft kinking	1.13	0.00	1.37E+69	1.00					1.13	0.00	1.37E+69	1.00

Multivariate analysis was conducted using the statistical programme SPSS. CI, confidence interval. HR, hazard ratio.

APP_23 Multivariate Cox proportional hazard model using the SPSS package, end of interval (variables P<0.1 included)

MULIVARIATE (SPSS)	ENTER				FORWARD				BACKWARD			
	95%CI				95%CI				95%CI			
Endpoint of the interval P<0.1	HR	Lower	Upper	P Value	HR	Lower	Upper	P Value	HR	Lower	Upper	P Value
Heart rate (b.p.m)	0.98	0.00	246.76	1.00					0.98	0.00	246.76	1.00
Serum haemoglobin (g/dl)	2.37	0.00	1.64E+17	0.97					2.37	0.00	1.64E+17	0.97
Ex- or current smoker	0.07	0.00	2.79E+32	0.94					0.07	0.00	2.79E+32	0.94
≥ 2 TV stented	0.00	0.00	5.58E+64	0.92					0.00	0.00	5.58E+64	0.92
Ipsilateral CIA deployment distance, mm	0.97	0.01	74.36	0.99					0.97	0.01	74.36	0.99
Contralateral limb diameter, mm	0.75	0.00	4.62E+06	0.97					0.75	0.00	4.62E+06	0.97
Preop bottom aortic neck diameter, mm	0.37	0.00	6.94E+05	0.89					0.37	0.00	6.94E+05	0.89
Preop (max) coronal neck angulation, °	0.94	0.08	10.81	0.96					0.94	0.08	10.81	0.96
Preop (max) CIA thrombus	24.31	0.00	1.08E+52	0.96					24.31	0.00	1.08E+52	0.96
1st bottom neck diameter, mm	1.19	0.00	8.77E+05	0.98					1.19	0.00	8.77E+05	0.98
1st contralateral CIA diameter, mm	1.11	0.00	5.58E+13	0.99					1.11	0.00	5.58E+13	0.99
1st aortic neck length, mm	0.56	0.01	36.73	0.79					0.56	0.01	36.73	0.79
1st caudal renal artery to bifurcation length, mm	0.98	0.09	10.87	0.99					0.98	0.09	10.87	0.99
Diameter change - coeliac axis, mm	0.76	0.00	1.85E+15	0.99					0.76	0.00	1.85E+15	0.99
Diameter change - cranial renal artery, mm	3.07	0.00	5.73E+08	0.91					3.07	0.00	5.73E+08	0.91
Diameter change - caudal renal artery, mm	0.47	0.00	1.37E+14	0.96					0.47	0.00	1.37E+14	0.96
Length change - SMA to cranial RA, mm	3.21	0.00	1.81E+05	0.83					3.21	0.00	1.81E+05	0.83
Length change - cranial RA to caudal RA, mm	2.76	0.00	8.75E+05	0.88					2.76	0.00	8.75E+05	0.88
Length change - caudal RA to aortic bif, mm	1.02	0.05	21.11	0.99					1.02	0.05	21.11	0.99
Graft kinking	959.35	0.00	5.97E+283	0.98					959.35	0.00	5.97E+283	0.98

Multivariate analysis was conducted using the statistical programme SPSS. CI, confidence interval. HR, hazard ratio.

APP_24 Comparison of Cox proportional hazards models for 1st CT aortic neck length variable (MI datasets)

			R (Enter)				SPSS (Enter)				SPSS (Forward)				SPSS (Backward)			
		Dataset	HR	95%CI		P value	HR	95%CI		P value	HR	95%CI		P value	HR	95%CI		P value
1st aortic neck length, mm	Beginning of interval	MI-1	0.90	0.84	0.98	0.01	0.91	0.84	0.98	0.01	0.91	0.85	0.98	0.01	0.91	0.85	0.98	0.01
		MI-2	0.91	0.84	0.98	0.02	0.91	0.84	0.98	0.02	0.92	0.85	0.98	0.01	0.92	0.85	0.98	0.01
		MI-3	0.90	0.84	0.98	0.01	0.91	0.84	0.98	0.01	0.91	0.85	0.98	0.01	0.91	0.85	0.98	0.01
		MI-4	0.91	0.84	0.98	0.01	0.91	0.84	0.98	0.01	0.92	0.85	0.98	0.02	0.91	0.85	0.98	0.01
		MI-5	0.90	0.84	0.98	0.01	0.91	0.84	0.98	0.01	0.91	0.85	0.98	0.01	0.91	0.85	0.98	0.01
	Midpoint of interval	MI-1	0.90	0.83	0.97	0.01	0.90	0.83	0.97	0.01	0.91	0.84	0.97	0.01	0.90	0.84	0.97	0.01
		MI-2	0.90	0.84	0.97	0.01	0.90	0.84	0.98	0.01	0.91	0.85	0.98	0.01	0.91	0.85	0.97	0.01
		MI-3	0.90	0.83	0.97	0.01	0.90	0.83	0.97	0.01	0.90	0.84	0.97	0.00	0.90	0.84	0.97	0.01
		MI-4	0.90	0.84	0.97	0.01	0.90	0.84	0.97	0.01	0.91	0.85	0.98	0.01	0.91	0.84	0.97	0.01
		MI-5	0.90	0.83	0.97	0.01	0.90	0.83	0.97	0.01	0.91	0.84	0.97	0.01	0.90	0.84	0.97	0.01
	End of interval	MI-1	0.90	0.83	0.97	0.01	0.90	0.83	0.97	0.01	0.91	0.84	0.98	0.01	0.90	0.84	0.97	0.01
		MI-2	0.90	0.89	0.92	0.04	0.90	0.84	0.98	0.01	0.91	0.85	0.98	0.01	0.91	0.85	0.98	0.01
		MI-3	0.90	0.83	0.97	0.01	0.90	0.83	0.97	0.01	0.90	0.84	0.97	0.01	0.90	0.84	0.97	0.01
		MI-4	0.90	0.84	0.97	0.01	0.90	0.84	0.98	0.01	0.91	0.85	0.98	0.01	0.91	0.84	0.97	0.01
		MI-5	0.90	0.83	0.97	0.01	0.90	0.83	0.97	0.01	0.91	0.84	0.97	0.01	0.90	0.84	0.97	<0.01
	Interval censoring	MI-1	0.90	0.80	0.96	<0.05												
		MI-2	0.90	0.80	0.96	<0.05												
		MI-3	0.90	0.79	0.94	<0.05												
		MI-4	0.90	0.81	0.95	<0.05												
		MI-5	0.90	0.80	0.96	<0.05												

MI, multiple imputations. CI, confidence interval. HR, hazard ratio.

APP_25 Comparison of Cox proportional hazards models for aortic diameter change at the coeliac axis variable (MI datasets)

			R (Enter)				SPSS (Enter)				SPSS (Forward)			SPSS (Backward)		
		Dataset	HR	95%CI		P value	HR	95%CI		P value	HR	95%CI	P value	HR	95%CI	P value
Aortic diameter change - coeliac axis, mm	Beginning of interval	MI-1	1.04	0.90	1.19	0.60	1.04	0.91	1.20	0.59						
		MI-2	1.06	0.92	1.12	0.41	1.06	0.92	1.20	0.42						
		MI-3	1.05	0.92	1.20	0.47	1.05	0.92	1.20	0.47						
		MI-4	1.05	0.91	1.20	0.53	1.05	0.91	1.20	0.53						
		MI-5	1.05	0.50	0.92	1.20	1.05	0.91	1.20	0.50						
	Midpoint of interval	MI-1	1.05	0.92	1.20	0.51	1.05	0.92	1.20	0.51						
		MI-2	1.07	0.93	1.22	0.35	1.07	0.93	1.20	0.35						
		MI-3	1.06	0.93	1.21	0.36	1.06	0.93	1.20	0.37						
		MI-4	1.05	0.92	1.20	0.45	1.05	0.92	1.20	0.45						
		MI-5	1.06	0.93	1.21	0.40	1.06	0.93	1.20	0.41						
	End of interval	MI-1	1.05	0.91	1.20	0.52	1.05	0.91	1.20	0.52						
		MI-2	1.07	0.54	2.12	0.35	1.07	0.93	1.23	0.35						
		MI-3	1.06	0.93	0.12	0.37	1.06	0.93	1.20	0.37						
		MI-4	1.06	0.92	1.21	0.44	1.06	0.92	1.20	0.44						
		MI-5	1.06	0.93	1.28	0.10	1.06	0.93	1.20	0.40						
	Interval censoring	MI-1	1.05	0.92	1.19	>0.05										
		MI-2	1.07	0.96	1.33	>0.05										
		MI-3	1.06	0.89	1.20	>0.05										
		MI-4	1.06	0.88	1.21	>0.05										
		MI-5	1.06	0.94	1.20	>0.05										

MI, multiple imputations. CI, confidence interval. HR, hazard ratio.

APP_26 Comparison of Cox proportional hazards models for follow-up aortic diameter change at caudal renal artery variable (MI datasets)

			R				SPSS (Enter)				SPSS (Forward)				SPSS (Backward)			
		Dataset	HR	95%CI		P value	HR	95%CI		P value	HR	95%CI		P value	HR	95%CI		P value
Aortic diameter change - caudal renal artery, mm	Beginning of interval	MI-1	1.14	1.01	1.30	0.04	1.14	1.00	1.29	0.04	**1.16**	**1.03**	**1.30**	**0.02**	**1.16**	**1.03**	**1.30**	**0.02**
		MI-2	1.16	1.01	1.32	0.03	1.15	1.01	1.30	0.04	**1.16**	**1.03**	**1.31**	**0.02**	**1.16**	**1.03**	**1.31**	**0.02**
		MI-3	1.16	1.02	1.33	0.07	1.15	1.01	1.31	0.04	**1.17**	**1.03**	**1.32**	**0.01**	**1.17**	**1.03**	**1.32**	**0.01**
		MI-4	1.14	1.01	1.30	0.04	1.14	1.00	1.29	0.05					**1.15**	**1.02**	**1.30**	**0.02**
		MI-5	1.15	1.01	1.31	0.07	1.14	1.01	1.30	0.04	1.13	1.00	1.26	0.05	**1.16**	**1.03**	**1.31**	**0.02**
	Midpoint of interval	MI-1	1.13	0.99	1.06	0.06	1.13	0.99	1.28	0.07					**1.15**	**1.02**	**1.29**	**0.03**
		MI-2	1.14	1.00	1.31	0.07	1.14	1.00	1.31	0.05					**1.16**	**1.02**	**1.31**	**0.02**
		MI-3	1.16	1.01	1.33	0.07	**1.16**	**1.01**	**1.33**	**0.03**	**1.13**	**1.00**	**1.28**	**0.04**	**1.18**	**1.03**	**1.34**	**0.01**
		MI-4	1.13	0.99	1.28	0.07	1.13	0.99	1.29	0.07					**1.15**	**1.02**	**1.29**	**0.03**
		MI-5	1.15	1.00	1.31	0.07	1.15	1.00	1.31	0.05	**1.13**	**1.00**	**1.28**	**0.04**	**1.16**	**1.02**	**1.31**	**0.02**
	End of interval	MI-1	1.10	0.97	1.25	0.07	1.10	0.97	1.25	0.14								
		MI-2	1.11	0.88	1.41	0.07	1.11	0.97	1.27	0.12								
		MI-3	1.13	0.98	1.29	0.07	1.13	0.99	1.29	0.08	**1.19**	**1.02**	**1.38**	**0.02**	**0.15**	**1.01**	**1.30**	**0.04**
		MI-4	1.10	0.97	1.26	0.14	1.10	0.97	1.26	0.14								
		MI-5	1.12	0.98	1.28	0.07	1.12	0.98	1.28	0.10	**1.13**	**1.00**	**1.28**	**0.04**	1.12	0.99	1.26	0.08
	Interval censoring	MI-1	1.10	0.94	1.25	>0.05												
		MI-2	1.11	0.92	1.29	>0.05												
		MI-3	1.13	0.95	1.36	>0.05												
		MI-4	1.10	0.94	1.28	>0.05												
		MI-5	1.12	0.98	1.30	>0.05												

MI, multiple imputations. CI, confidence interval. HR, hazard ratio.

APP_27 Comparison of Cox proportional hazards models for contralateral limb diameter variable (MI datasets)

			R (Enter)				SPSS (Enter)				SPSS (Forward)				SPSS (Backward)			
		Dataset	HR	95%CI		P value	HR	95%CI		P value	HR	95%CI		P value	HR	95%CI		P value
Contralateral iliac limb diameter, mm	Beginning of interval	MI-1	0.85	0.74	0.99	0.03	0.86	0.74	0.99	0.04	0.86	0.75	0.99	0.04	0.86	0.75	0.99	0.04
		MI-2	0.84	0.72	0.98	0.03	0.85	0.73	0.99	0.03	0.86	0.74	0.99	0.04	0.86	0.74	0.99	0.04
		MI-3	0.81	0.70	0.94	0.01	0.82	0.70	0.95	0.01	0.83	0.72	0.95	0.10	0.83	0.72	0.95	0.01
		MI-4	0.83	0.71	0.96	0.01	0.83	0.72	0.97	0.02	0.83	0.72	0.95	0.01	0.84	0.72	0.97	0.02
		MI-5	0.82	0.70	0.95	0.01	0.82	0.71	0.96	0.01	0.83	0.72	0.96	0.01	0.83	0.72	0.96	0.01
	Midpoint of interval	MI-1	0.85	0.73	0.98	0.03	0.85	0.73	0.98	0.03	0.88	0.78	1.00	0.05	0.86	0.75	0.99	0.04
		MI-2	0.83	0.71	0.97	0.02	0.83	0.71	0.97	0.02	0.87	0.77	0.99	0.04	0.85	0.74	0.99	0.03
		MI-3	0.79	0.68	0.93	0.01	0.79	0.68	0.93	0.01	0.82	0.70	0.95	0.01	0.82	0.70	0.95	0.01
		MI-4	0.82	0.70	0.96	0.01	0.82	0.71	0.96	0.01	0.86	0.76	0.97	0.02	0.84	0.72	0.97	0.02
		MI-5	0.81	0.69	0.94	0.01	0.81	0.69	0.94	0.01	0.83	0.72	0.95	0.01	0.83	0.71	0.96	0.01
	End of interval	MI-1	0.84	0.72	0.98	0.03	0.84	0.72	0.98	0.03	0.91	0.84	0.98	0.05	0.87	0.77	0.99	0.04
		MI-2	0.82	0.80	0.84	0.08	0.82	0.70	0.96	0.02	0.87	0.77	0.99	0.04	0.86	0.76	0.98	0.03
		MI-3	0.79	0.67	0.93	0.01	0.79	0.67	0.93	0.00	0.82	0.70	0.95	0.01	0.81	0.70	0.94	0.01
		MI-4	0.81	0.70	0.95	0.01	0.81	0.70	0.95	0.01	0.86	0.76	0.97	0.02	0.85	0.74	0.97	0.01
		MI-5	0.80	0.68	0.94	0.01	0.80	0.68	0.94	0.01	0.83	0.72	0.95	0.01	0.82	0.71	0.95	0.01
	Interval censoring	MI-1	0.84	0.68	0.95	<0.05												
		MI-2	0.82	0.64	0.92	<0.05												
		MI-3	0.79	0.59	0.98	<0.05												
		MI-4	0.81	0.59	0.88	<0.05												
		MI-5	0.80	0.61	0.91	<0.05												

MI, multiple imputations. CI, confidence interval. HR, hazard ratio.

APP_28 Comparison of Cox proportional hazards models for Ipsilateral limb deployment distance variable (MI datasets)

			R (Enter)				SPSS (Enter)				SPSS (Forward)			SPSS (Backward)		
		Dataset	HR	95%CI		P value	HR	95%CI		P value	HR	95%CI	P value	HR	95%CI	P value
Ipsilateral limb deployment distance, mm	Beginning of interval	MI-1	1.02	0.99	1.06	0.20	1.02	0.99	1.06	0.22						
		MI-2	1.03	1.00	1.07	0.08	1.03	1.00	1.07	0.09						
		MI-3	1.03	0.99	1.07	0.09	1.03	0.99	1.06	0.12						
		MI-4	1.02	0.99	1.06	0.17	1.02	0.99	1.06	0.18						
		MI-5	1.03	0.99	1.06	0.14	1.03	0.99	1.06	0.16						
	Midpoint of interval	MI-1	1.02	0.99	1.06	0.22	1.02	0.99	1.06	0.22						
		MI-2	1.03	0.99	1.07	0.10	1.03	1.00	1.07	0.10						
		MI-3	1.03	0.99	1.07	0.10	1.03	0.99	1.07	0.11						
		MI-4	1.02	0.99	1.06	0.20	1.02	0.99	1.06	0.20						
		MI-5	1.03	0.99	1.06	0.15	1.03	0.99	1.06	0.15						
	End of interval	MI-1	1.02	0.98	1.05	0.40	1.02	0.98	1.05	0.37						
		MI-2	1.02	0.65	1.60	0.20	1.02	0.99	1.06	0.23						
		MI-3	1.02	0.99	1.06	0.26	1.02	0.99	1.06	0.26						
		MI-4	1.01	0.98	1.05	0.42	1.02	0.98	1.05	0.42						
		MI-5	1.02	0.98	1.05	0.32	1.02	0.98	1.06	0.32						
	Interval censoring	MI-1	1.02	0.99	1.06	>0.05										
		MI-2	1.02	1.00	1.06	>0.05										
		MI-3	1.02	1.00	1.07	>0.05										
		MI-4	1.01	0.99	1.06	>0.05										
		MI-5	1.02	0.98	1.06	>0.05										

MI, multiple imputations. CI, confidence interval. HR, hazard ratio.

APP_29 Comparison of Cox proportional hazards models for the graft kinking variable (MI datasets)

			R (Enter)				SPSS (Enter)				SPSS (Forward)			SPSS (Backward)		
		Dataset	HR	95%CI		P value	HR	95%CI		P value	HR	95%CI	P value	HR	95%CI	P value
Graft kinking	Beginning of interval	MI-1	1.44	0.55	3.81	0.46	0.71	0.27	1.88	0.49						
		MI-2	1.46	0.55	3.87	0.45	0.72	0.27	1.90	0.51						
		MI-3	1.38	0.52	3.65	0.51	0.77	0.29	2.05	0.61						
		MI-4	1.48	0.56	3.91	0.43	0.71	0.27	1.87	0.48						
		MI-5	1.45	0.55	3.84	0.45	0.72	0.27	1.91	0.52						
	Midpoint of interval	MI-1	1.69	0.63	4.55	0.30	0.59	0.22	1.60	0.30						
		MI-2	1.74	0.65	4.71	0.27	0.58	0.21	1.55	0.28						
		MI-3	1.75	0.66	4.67	0.26	0.58	0.22	1.53	0.27						
		MI-4	1.76	0.66	4.71	0.26	0.57	0.21	1.53	0.27						
		MI-5	1.78	0.67	4.73	0.25	0.57	0.21	1.51	0.26						
	End of interval	MI-1	1.73	0.63	4.72	0.29	0.58	0.21	1.58	0.29						
		MI-2	1.83	0.41	2.93	0.52	0.55	0.20	1.50	0.24						
		MI-3	0.95	0.89	1.02	0.19	0.55	0.21	1.48	0.24						
		MI-4	1.78	0.66	4.81	0.25	0.56	0.21	1.51	0.25						
		MI-5	1.80	0.67	4.83	0.24	0.55	0.21	1.83	0.24						
	Interval censoring	MI-1	1.73	0.52	5.50	>0.05										
		MI-2	1.85	0.33	6.02	>0.05										
		MI-3	1.84	0.47	4.66	>0.05										
		MI-4	1.80	0.43	4.53	>0.05										
		MI-5	1.82	0.50	7.60	>0.05										

MI, multiple imputations. CI, confidence interval. HR, hazard ratio.

APP_30 Comparison of Cox proportional hazards models for change in length – SMA to cranial renal artery variable (MI datasets)

			R (Enter)				SPSS (Enter)				SPSS (Forward)				SPSS (Backward)			
		Dataset	HR	95%CI		P value	HR	95%CI		P value	HR	95%CI		P value	HR	95%CI		P value
Change in length - SMA to cranial renal artery, mm	Beginning of interval	MI-1	0.93	0.87	0.99	0.03	0.88	0.80	0.97	0.01	0.92	0.87	0.99	0.02	0.92	0.87	0.99	0.02
		MI-2	0.92	0.86	0.99	0.02	0.93	0.87	0.99	0.03	0.92	0.86	0.98	0.01	0.92	0.86	0.98	0.01
		MI-3	0.93	0.87	0.99	0.02	0.93	0.87	0.99	0.02	0.92	0.86	0.98	0.01	0.92	0.86	0.98	0.01
		MI-4	0.93	0.87	1.00	0.04	0.93	0.87	1.00	0.05					0.92	0.87	0.99	0.02
		MI-5	0.94	0.88	1.00	0.06	0.94	0.88	1.00	0.07	0.93	0.87	0.99	0.03	0.93	0.87	0.99	0.03
	Midpoint of interval	MI-1	0.94	0.88	1.01	0.10	0.89	0.81	0.99	0.03	0.88	0.80	0.96	0.01	0.93	0.87	1.00	0.04
		MI-2	0.94	0.87	1.01	0.08	0.94	0.88	1.01	0.08					0.93	0.87	0.99	0.02
		MI-3	0.94	0.88	1.00	0.07	0.94	0.88	1.01	0.07	0.93	0.87	0.99	0.02	0.93	0.87	0.99	0.02
		MI-4	0.95	0.88	1.01	0.11	0.95	0.88	1.01	0.11					0.93	0.87	1.00	0.03
		MI-5	0.95	0.89	1.02	0.17	0.95	0.89	1.02	0.17					0.94	0.88	1.00	0.07
	End of interval	MI-1	0.96	0.89	1.03	0.26	0.91	0.82	1.01	0.07	0.88	0.80	0.96	0.01				
		MI-2	0.96	0.61	1.50	0.04	0.96	0.89	1.03	0.23								
		MI-3	0.95	0.89	1.02	0.19	0.95	0.89	1.02	0.19	0.93	0.87	0.99	0.02	0.94	0.88	1.01	0.07
		MI-4	0.96	0.89	1.03	0.28	0.96	0.89	1.03	0.28								
		MI-5	0.97	0.90	1.04	0.39	0.97	0.90	1.04	0.39								
	Interval censoring	MI-1	0.96	0.89	1.03	>0.05												
		MI-2	0.96	0.87	1.02	>0.05												
		MI-3	0.95	0.88	1.00	>0.05												
		MI-4	0.96	0.85	1.00	>0.05												
		MI-5	0.97	0.90	1.03	>0.05												

MI, multiple imputations. CI, confidence interval. HR, hazard ratio.

R Code

Kaplan Meier survival analysis using the beginning of the interval

```
library(survival)
mydata=read.csv("filename.csv")
mysurv=Surv(mydata$beginning, mydata$event)
plot(survfit(my.surv~1), yscale=100, xaxp =c(0,48,4), xlim=c(1,48), yaxs="i", frame.plot=F)
title(main="Type of analysis", sub="",
      xlab="Time from 1st follow-up CT scan, months", ylab="Cumulative survival")
summary(survfit(my.surv~1), times=c(6, 12, 24, 36, 48))
```

Kaplan Meier survival analysis using the midpoint of the interval

```
library(survival)
mydata=read.csv("filename.csv")
mysurv=Surv(mydata$midpoint, mydata$event)
plot(survfit(my.surv~1), yscale=100, xaxp =c(0,48,4), xlim=c(1,48), yaxs="i", frame.plot=F)
title(main="Type of analysis", sub="",
      xlab="Time from 1st follow-up CT scan, months", ylab="Cumulative survival")
summary(survfit(my.surv~1), times=c(6, 12, 24, 36, 48))
```

Kaplan Meier survival analysis using the end of the interval

```
library(survival)
mydata=read.csv("filename.csv")
mysurv=Surv(mydata$end, mydata$event)
plot(survfit(my.surv~1), yscale=100, xaxp =c(0,48,4), xlim=c(1,48), yaxs="i", frame.plot=F)
title(main="Type of analysis", sub="",
      xlab="Time from 1st follow-up CT scan, months", ylab="Cumulative survival")
summary(survfit(my.surv~1), times=c(6, 12, 24, 36, 48))
```

Kaplan_Meier survival analysis, using interval censoring

```
library(survival)

mydata=read.csv("filename.csv")

mysurv=Surv(mydata$left, mydata$right, type="interval2")

plot(survfit(my.surv~1), yscale=100, xaxp =c(0,48,4), xlim=c(1,48), yaxs="i", frame.plot=F)

title(main="Type of analysis", sub="",

      xlab="Time from 1st follow-up CT scan, months", ylab="Cumulative survival")

summary(survfit(my.surv~1), times=c(6, 12, 24, 36, 48))
```

Cox proportional hazards model using the beginning of the interval

```
library(survival)

mydata=read.csv("filename.csv")

coxph(formula = Surv(beginning, event) ~ variable1 +variable2 + factor(variable3) +variable4
+ variable5 + variable6,data = mydata)
```

Cox proportional hazards model using the midpoint of the interval

```
library(survival)

mydata=read.csv("filename.csv")

coxph(formula = Surv(midpoint, event) ~ variable1 +variable2 + factor(variable3) +variable4 +
variable5 + variable6,data = mydata)
```

Cox proportional hazards model using the end of the interval

```
library(survival)

mydata=read.csv("filename.csv")

coxph(formula = Surv(end, event) ~ variable1 +variable2 + factor(variable3) +variable4 +
variable5 + variable6, data = mydata)
```

Cox proportional hazards model using interval censoring

```
library(intcox)

mydata=read.csv("filename,csv")

intcox(Surv(left,right, type="interval2") ~ variable1 +variable2 + factor(variable3) +variable4 +
variable5 + variable6, data=mydata, na.action=na.pass)
```

Bootstrapping technique to generate 95%CI for Intcox hazard ratios

```
n=100

co=matrix(0,n,6)


for (i in seq(1,100)){


databoot=data[sample(nrow(data),size=length(data[,1]),replace=TRUE),]

databoot=databoot[order(databoot[,1]),1:20]

sol=intcox(Surv(left, right, type="interval2")~ variable1 +variable2 + factor(variable3)
+variable4 + variable5 + variable6, data=databoot, na.action=na.pass)

co[i,]=sol$coef

}


variable1_lower_95CI=sort(co[,1])[3]

variable1_upper_95CI=sort(co[,1])[97]

variable2_lower_95CI=sort(co[,2])[3]

variable2_upper_95CI=sort(co[,2])[97]

variable3_lower_95CI=sort(co[,3])[3]

variable3_upper_95CI=sort(co[,3])[97]

variable4_lower_95CI=sort(co[,4])[3]

variable4_upper_95CI=sort(co[,4])[97]

variable5_lower_95CI=sort(co[,5])[3]
```

variable5_upper_95CI=sort(co[,5])[97]

variable6_lower_95CI=sort(co[,6])[3]

variable6_upper_95CI=sort(co[,6])[97]

variable1_lower_95CI

variable1_upper_95CI

variable2_lower_95CI

variable2_upper_95CI

variable3_lower_95CI

variable3_upper_95CI

variable4_lower_95CI

variable4_upper_95CI

variable5_lower_95CI

variable5_lower_95CI

variable6_lower_95CI

variable6_upper_95CI