SURVEILLANCE FOLLOWING ENDOVASCULAR REPAIR OF ABDOMINAL AORTIC ANEURYSM

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by

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Dedication:

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PRIZES, PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS WORK

Prizes

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Publications

Prospective, single UK centre, comparative study of the predictive values of contrast-enhanced ultrasound compared to time-resolved CT angiography in the detection and characterisation of endoleaks in high-risk patients undergoing endovascular aneurysm repair surveillance: a protocol.

Roy IN, Chan TY, Czanner G, et al. BMJ Open 2018;8:e020835.

National & International Presentations

Sol Cohen Prize Session: The true graft related endoleak detection rate of contrast enhanced ultrasound: A prospective single UK centre study of the predictive values of contrast enhanced ultrasound compared to time-resolved CTA

Vascular Society of Great Britain & Ireland, Manchester, UK, November 2019

Achieving compliance with post-operative EVAR surveillance and analysis of factors that influence individual patient conformity, a single tertiary UK centres' experience

Vascular Society of Great Britain & Ireland, Manchester, UK, November 2019

Personalised Medicine: Individualised intervals to next EVAR surveillance visit. Development and validation of a stable and highly predictive model of future risk of requiring a secondary intervention

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Critical Issues in Endo-grafting, Liverpool UK, May 2019

The true graft related endoleak detection rate of contrast enhanced ultrasound: A prospective single UK centre study of the predictive values of contrast enhanced ultrasound compared to time-resolved CTA

British Society of Endovascular Therapy, Gloucestershire, UK, June 2018

Profile of Secondary Interventions and Triggering Surveillance Imaging after EVAR
Cardiovascular and Interventional Radiology Society of Europe, Copenhagen Denmark, September 2017

Personalised EVAR Surveillance Based on Stratification of Individual Patient Risk of Secondary Intervention From Readily Measurable Surveillance Parameters
European Society of Vascular Surgery, Lyon France, September 2017
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Abstract published: Roy, I. et al. European Journal of Vascular and Endovascular Surgery, Volume 54, Issue 5, 668

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iMeet Congress, Nice France, June 2017

Personalised EVAR Surveillance Based on Stratification of Individual Patient Risk of Secondary Intervention From Readily Measurable Surveillance Parameters
CX Symposium, London UK, April 2017

Compliance with Surveillance following EVAR
British Society of Endovascular Therapy, Warwickshire, UK, June 2016

Profile of Secondary Interventions and Triggering Surveillance Imaging after EVAR
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iMEET Congress, Nice, France, June 2016

ABSTRACT

Introduction

Endovascular Aneurysm Repair (EVAR) is the commonest form of repair of Abdominal Aortic Aneurysms (AAA). EVAR involves the placement of a stent-graft that seals into the arteries proximally and distally containing blood flow through the AAA. EVAR suffers from complications and treatment failures and patients are enrolled on a surveillance programme to identify these so corrective secondary intervention might be undertaken. Surveillance contributes significantly to the cost of treatment and is inefficient.

Efficient surveillance requires adequate knowledge of the; nature and timing of complications, diagnostic merits of surveillance imaging, factors which limit patient compliance and ability to predict the risk of future complications. This work addresses deficiencies in these areas.

Methods

A database of a city wide vascular surgical service and surveillance imaging reports for 2008-15 were analysed under ethical approved. The nature / incidence of secondary interventions and degree of compliance with surveillance were reported using descriptive statistics and incidence. Association between patient factors and non-compliance were examined using adjusted odds ratios (AOR).

Missing datapoints in imaging data were addressed using multiple imputation utilising chained equations. Surveillance imaging findings were assessed for association with subsequent secondary intervention using Kaplan-Myer plots, log rank test and AORs. AOR were calculated using multivariate models.

A piecewise exponential model (PEM) was created to predict future risk of secondary intervention at different times following EVAR. This was internally validated using a bootstrapping technique and assessed using Hosmer–Lemeshow test and receiver operator characteristics (ROC).

A prospective imaging study of Contrast Enhanced Ultrasound Scan (CEUS) and time-resolved Computer Tomography Angiography (tCTA) was undertaken, the diagnostic values of CEUS to diagnose a graft-related endoleak were obtained.

Results

A total of 2901 patient years of follow-up in 756 individuals were analysed. The intended purpose of the 178 secondary interventions was, 85(48%) maintaining distal perfusion and 93(52%) maintaining effective aneurysm treatment. The incidence of secondary interventions following EVAR varied at different stages of follow-up between approximately 35 and 60 interventions per 1000 patient years.

Compliance was maintained above 95% until 10 years after EVAR. The factors most associated with compliance were; years after EVAR (AOR 0.62), calendar year EVAR performed (0.67), age at time (0.96) and previously undergone a secondary intervention (1.13).

Evaluation of Colour Duplex Ultrasound Scan (CDUS) and Abdominal Radiography (AXR) findings demonstrated that reducing the number of collected findings did not lead to changes in the overall association with secondary intervention.

Internal validation of the PEM model demonstrated an area under the curve of 0.72 (95% CI 0.68 – 0.76) on ROC analysis and Hosmer–Lemeshow test produced a median p-value of 0.51, demonstrating satisfactory discrimination and calibration.

On blinded prospective study CEUS has a sensitivity of 0.56 (95% confidence interval 0.23 – 0.88) and specificity of 0.90 (0.78 – 1.00) to diagnose a graft related endoleak, with tCTA as the comparator standard.

Conclusion

This work demonstrates the changing epidemiology of secondary interventions after EVAR, that CDUS & AXR reporting can be simplified and those findings can be used to predict future risk of secondary interventions. Excellent compliance with EVAR surveillance is achievable and is associated with a small number of patient factors. Finally, CEUS is demonstrated to have poor graft related endoleak diagnostic values when compared to tCTA.

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List of Abbreviations and Acronyms

AAA	Abdominal Aortic Aneurysm
AUC	Area Under the Curve
AXR	Abdominal Radiograph [X-Ray]
CDUS	Colour Doppler Ultrasound Scan
CEUS	Contrast Enhanced Ultrasound Scan
CI	Confidence Interval
CT	Computer Tomography
CTA	Computer Tomography Angiography
tCTA	time-resolved Computer Tomography Angiography
DSA	Digital Subtraction Angiography
EVAR	Endovascular Aneurysm Repair
HES	Hospital Episode Statistics
HI	Harmonic Imaging
IFU	Instructions For Use
IQR	Inter-Quartile Range
LiVES	Liverpool Vascular and Endovascular Service
NMAR	Not Missing At Random
MAGIC	The Management of Aortic Graft Infection Collaboration
MAR	Missing At Random
MPR	Multi Planar Reconstruction
MRA	Magnetic Resonance Angiogram
NHS AAA SP	National Health Service AAA Screening Programme
ONS	Office for National Statistics
OSR	Open Surgical Repair
PEM	Piecewise Exponential Model
PII	Pulse Inversion Imaging
PSV	Peak Systolic Velocity
RCT	Randomised Controlled Trial
ROC	Receiver Operating Characteristic
STARD	Standards for Reporting of Diagnostic Accuracy Studies
WHO	World Health Organisation
2D / 3D	Two Dimensional / Three Dimensional

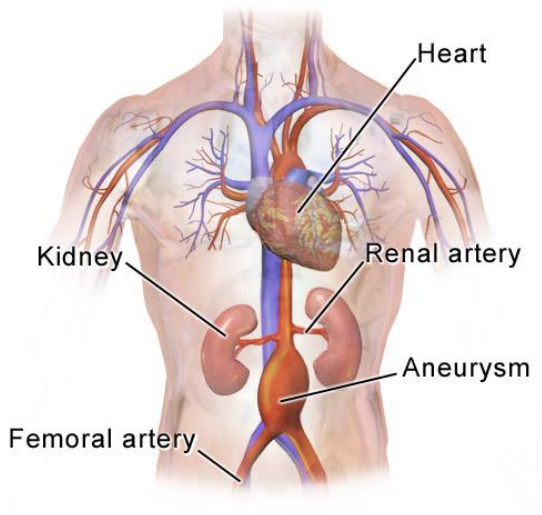
1 Introduction: Abdominal Aortic Aneurysms, Endovascular Repair and Subsequent Surveillance

The aorta is the largest artery in the body. It can, as the result of deterioration or injury, dilate to form an aneurysm. The commonest site of an aortic aneurysm is in the abdomen, below the renal arteries. Abdominal aortic aneurysms (AAA) grow over time and can rupture, leading to haemorrhage and often resulting in death. Prophylactic repair of AAA has been developed to prevent such deaths. The most common method of prophylactic repair in the United Kingdom is Endovascular Aneurysm Repair (EVAR). EVAR involves the placement of a stent-graft into the aneurysm, under X-ray guidance, in a minimally invasive manner. The EVAR stent-graft seals proximally and distally and carries the contained blood through the aneurysm, so preventing rupture. EVAR is imperfect and there is a rate of failure of the stent-grafts implanted, it is therefore recommended all patients undergoing EVAR should be enrolled on to a regimen of surveillance imaging to detect such failures, so corrective secondary interventions might be undertaken. The best imaging modality and regimen for EVAR surveillance is not yet fully understood.

1.1 Abdominal Aortic Aneurysms

Abdominal aortic aneurysm (AAA) is a dilatation of the largest artery in the abdomen and the commonest position of an AAA is inferior to the renal arteries, Figure 1 (page 2). AAA is conventionally defined as an aorta of diameter greater than 30mm. [1-3] The most common alternative definition is an aortic diameter 150% of the adjacent normal segment diameter, this definition has the benefit of accounting for individual and sex variance in normal aortic diameter. [4 5]

Figure 1: Infrarenal Abdominal Aortic Aneurysm



The major vessels of the trunk with an aneurysm of the aorta below the renal arteries.
Credit: Blausen Medical Communications, Inc. Reproduced under the CC BY-SA 4.0 License

1.1.1 Prevalence

The prevalence of AAAs has been investigated by several screening studies of selected populations. Two large UK studies provided the main evidence base for the creation of the National Health Service Abdominal Aortic Aneurysm Screening Programme (NHSAAASP), which in turn provides contemporary information on AAA prevalence in 65 year old males in the UK.

Scott et al. undertook a randomised control trial of screening for AAA in Chichester, UK and the surrounding district between 1988 and 1990.[6] 15,775 male and female patients between 65 and 80 years old were randomised to invitation to undergo ultrasound screening for AAA or no invitation. Of the 5394 who attended for ultrasound AAA screening, 218 (4.0%) had an AAA detected on the initial screening. There was a marked difference in AAA prevalence between sexes, with 178 of 2342 (7.6%) screened

males having an aneurysm compared to 40 of 3052 (1.3%) of females. This low incidence in the female population has been confirmed on systematic review and meta-analysis of contemporary studies in which screening was performed after the year 2000.[7] The second UK screening study was the Multicentre Aneurysm Screening Study; they randomised 67,770 men aged 65-74 to either invitation to ultrasound aneurysm screening or a control group who were not invited. 1,333 men had an aneurysm detected out of 27,147 who attended for surveillance, a prevalence of 4.9%.[8] The NHSAAASP is available for all men aged 65 and over, in England. In 2016/17 the NHSAAASP invited 281,965 men to screening at the age of 65. 228,563 underwent ultrasound surveillance and 2,471 had an AAA diagnosed, a prevalence of 1.1%.[9]

1.1.2 Natural History (Expansion Rates and Rupture Risk)

AAAs expand over time and have a corresponding increasing risk of rupture the larger they are. Expansion (measured as an increase in diameter) is best estimated using statistical likelihood methods (rather than linear regression) as patients are typically referred to treatment following their first measurement that is in excess of the treatment threshold.[10] This means that any over estimation at final measurement is not corrected for by future measurements and leads to an over estimation of the overall expansion rate using linear regression modelling. Serial Aneurysm measurements from the UK Small Aneurysm Trial,[11] is the largest series of UK data to have been analysed in this manner. Brady et al,[12] demonstrated a mean expansion rate of 2.6mm a year (95% confidence interval (CI) 2.5-2.6 mm/year) when fitted to a linear likelihoods model, there is however a large variation between individuals, 95% reference range -1.0 to 6.1 mm/year. When fitted to the more appropriate quadratic model the coefficient on the mean quadratic term for time was 0.11mm/year, 95% CI 0.07-0.16. [13] Expansion rates in the linear model were not associated with age or sex but were associated with diameter at baseline, aneurysms expanded 1.29mm/year (95% CI 1.05-1.35) faster for every 10mm larger they were at baseline. Current smokers also had an increased rate of expansion of 0.42mm/year (95% CI 0.17-0.68) when compared to ex-smokers. This association is present even after adjustment for potential confounding factors. Hypertension, systolic blood pressure at baseline, anti-hypertensive medication, ischemic heart disease on ECG, body mass index (BMI), total cholesterol, white cell count, triglycerides and HDL Cholesterol were not associated with expansion rates.

Larger aneurysms are more likely to rupture, has been observed in several studies.[14-16] European guidelines[17] have summarised this risk (stratified by size), Table 1 (page 4), contemporary data from the NHSAAASP has shown that men over 65 with a 30-44mm diameter AAA have a rupture risk of 0.03% per an annum and those with a AAA 45-55mm diameter AAA only have 0.28% per annum risk of rupture.[18] These much lower risks could be the result of improved medical management of cardiovascular risk factors or changes in lifestyle in the population. The factors known to be associated with increased risk of AAA rupture is also associated with female sex,[19-21] smoking,[22] hypertension,[19 20 23] and rate of AAA expansion.[20 24-26] The strength of evidence supporting these associations is variable and not as strong as the association with size.

Table 1: Abdominal Aortic Aneurysm Rupture Risk by Diameter

Abdominal Aortic Aneurysm Diameter (mm)	Risk of Rupture in 12 Months (%)
30-39	0
40-49	1.0
50-59	1.0-11
60-69	10-22
>70	30-33

Credit: Created from data in *Eur J Vasc Endovasc Surg* 2011;41 Suppl 1:S1-S58. doi: 10.1016/j.ejvs.2010.09.011

1.1.3 Rationale and Evidence for Repair

Repair of AAA is undertaken to prevent a premature death from rupture. As such the risk of death without AAA repair should be higher than the risk of death of and after undergoing AAA repair. The risk of death following AAA rupture is in excess of 80% - when emergency AAA repair is available,[27] this multiplied by the risk of rupture, added to the patients risk of mortality from other causes calculates their risk of mortality without repair. The risk of mortality with AAA repair is: the risk of mortality associated with the AAA repair, any persistent risk of AAA mortality following repair added to the patients risk of mortality from other causes. As the patient's risk of mortality from other causes falls on both sides of this equation it could, for simplicity, be discounted to create an AAA mortality only consideration. The risk of rupture vs the risk of repair, are

the dominate factors in such a calculation, in clinical practice the risk of AAA rupture is quantified by AAA size and rates of change thereof. These were studied in the "UK Small Aneurysm Trial" and the "American Aneurysm Detection And Management Study" where patients with asymptomatic AAAs between 40 - 55mm where randomised to immediate open surgical repair or continued AAA surveillance and repair at a 55mm threshold. A Cochrane review analysis of participant level data showed that repair below 55mm was not associated with improved survival, compared to continued surveillance and considered repair at 55mm, with a hazard ratio of 0.99 (95% CI 0.83-1.18). [28]

In the UK patients with an AAA larger than 55mm are routinely offered repair if they are physiologically fit to undergo such a repair. Such patients are assessed on a total mortality with and without AAA repair basis. Aneurysm size (and therefore rupture risk) has significant influence, however patient physiological status both to withstand surgical repair (mortality risk at time of repair) and the overall patient life expectancy without repair will significantly influence this judgement. This is a complex calculation that often relies on an element of physician intuition and experience. Several predictive risk models have been proposed but none have entered clinical use. The more recent British Aneurysm Repair Score looks to have much better discrimination and if confirmed on validation studies would offer a more standardised approach to the decision making process.[29]

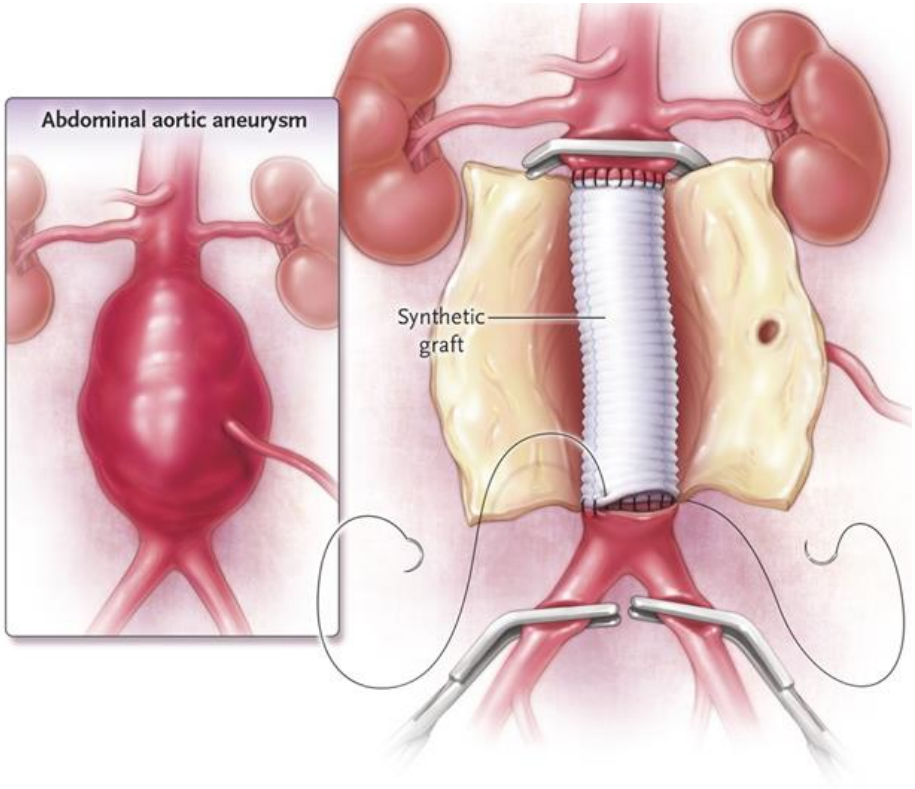
1.2 Open Surgical Repair

The first open surgical repair (OSR) of AAA that approximates current technique was reported by Dubost et al. in 1951, where the aortic aneurysm was totally resected and replaced with a cadaveric homograft.[30] DeBakey substituted the use of homografts with polyester fabric tubes in the same aneurysm resection technique in 1958.[31] This was refined to an inlay technique, removing the need for aneurysm resection, by Creech in 1966 and popularised in the UK by Orr and Davies in 1974.[32] [33] The inlay technique remains the standard of care for OSR, a laparotomy and retroperitoneal dissection are performed to allow clamping of the aorta proximal and the iliac arteries distal to the AAA. The aneurysm is then opened anteriorly and the origin of any bleeding aortic side branches are over sewn. A synthetic graft is then laid into the AAA and anastomosed to the aorta proximally and either the aorta or iliac arteries distally, Figure 2 (page 6). The

aneurysm is then closed over the synthetic graft, retroperitoneum closed and laparotomy closure completed.

OSR is a major operation that has significant associated morbidity and mortality, a 2017 UK audit demonstrated an in hospital mortality of 3.2% and 5.5% of patients were readmitted to hospital within 30 days. This mortality is a significant improvement on the 6.7% mortality rate reported in 2001 by the UK National Vascular Database which had not significantly improved in the previous 21 years in some centres.[34] The improvement from 6.7% to 3.2% may represent a difference in case selection as a result of wider uptake of EVAR for higher risk cases.

Figure 2: Open Surgical Repair of an Abdominal Aortic Aneurysm



Intact Abdominal Aortic Aneurysm and depiction of partially completed open surgical repair: demonstrating a proximal aortic clamp just below the renal arteries, a completed proximal anastomosis of aorta to synthetic graft, a partial completed distal anastomosis and distal clamps on the iliac arteries. **Credit:** DOI:10.1056/NEJMcp1401430 [35] Reproduced with permission, ©Massachusetts Medical Society

OSR is a durable procedure with only 0.9 aneurysm related deaths per 100 patient years in the 15 years follow-up of the UK EVAR trial 1.[36] Overall (all cause) mortality following OSR was 8.9 deaths per 100 patient years. The rate of secondary intervention (complications) was 1.0 per 100 patient years confirming previous study's observations

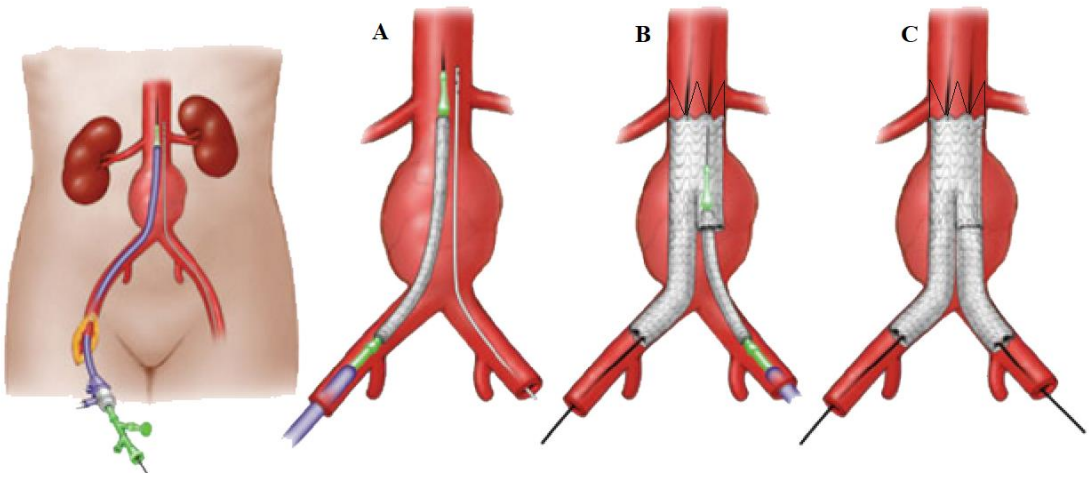
regarding OSR durability.[37] The UK EVAR trial 1 did, however, initially fail to record common incision related complications such as hernias.

1.3 Endovascular Aneurysm Repair

In 1991 Volodos et al. and Parodi et al., independently, proposed EVAR as a new treatment for AAA based on the principles of endovascular interventions.[38 39] EVAR is designed to exclude pressurised blood flow from the AAA wall, therefore excluding the possibility of rupture. During EVAR a stent graft is inserted under fluoroscopic X-ray guidance into the aorta. It achieves its therapeutic aim by being deployed and sealing into healthy artery proximal and distal to the AAA, as such the blood is transmitted through the stent-graft, which lies within the aneurysm, without pressurising the AAA. In vascular interventions a stent-graft is distinguished from a [simple] stent by the intent of its use, a stent graft is intended to replace the function of a portion of vessel while a stent is a scaffold placed inside a vessel to relieve an obstruction. Stent-grafts always consist of a fabric tube with various forms of structural support while stents typically do not have of a fabric tube, although may contain fabric in some circumstances.

The main stages of a standard EVAR procedure are depicted, Figure 3 (page 7). Initially transfemoral access is obtained by either percutaneous ultrasound guided puncture or surgical exposure and direct puncture of the common femoral arteries. A wire is used to transverse the aneurysm (distal to proximal) under fluoroscopic guidance. The main body of the stent graft is then positioned at the proximal landing zone via one femoral and a catheter via the other femoral. The catheter is used to inject contrast material to define the origins of the renal arteries, which is the proximal most point of the landing zone. The main body of the stent graft is then deployed creating a seal proximally and normally extends and seals into the iliac vessel down one limb of the EVAR. The contra-lateral limb is relatively short, this limb is then cannulated via the contralateral femoral artery access point, that previously conveyed the contrast catheter. The contralateral limb extension is then placed inside the short limb of the body component and deployed, it seals within the short limb proximally and the iliac artery distally.

Figure 3: Stages of a Bifurcated Endovascular Aneurysm Repairt



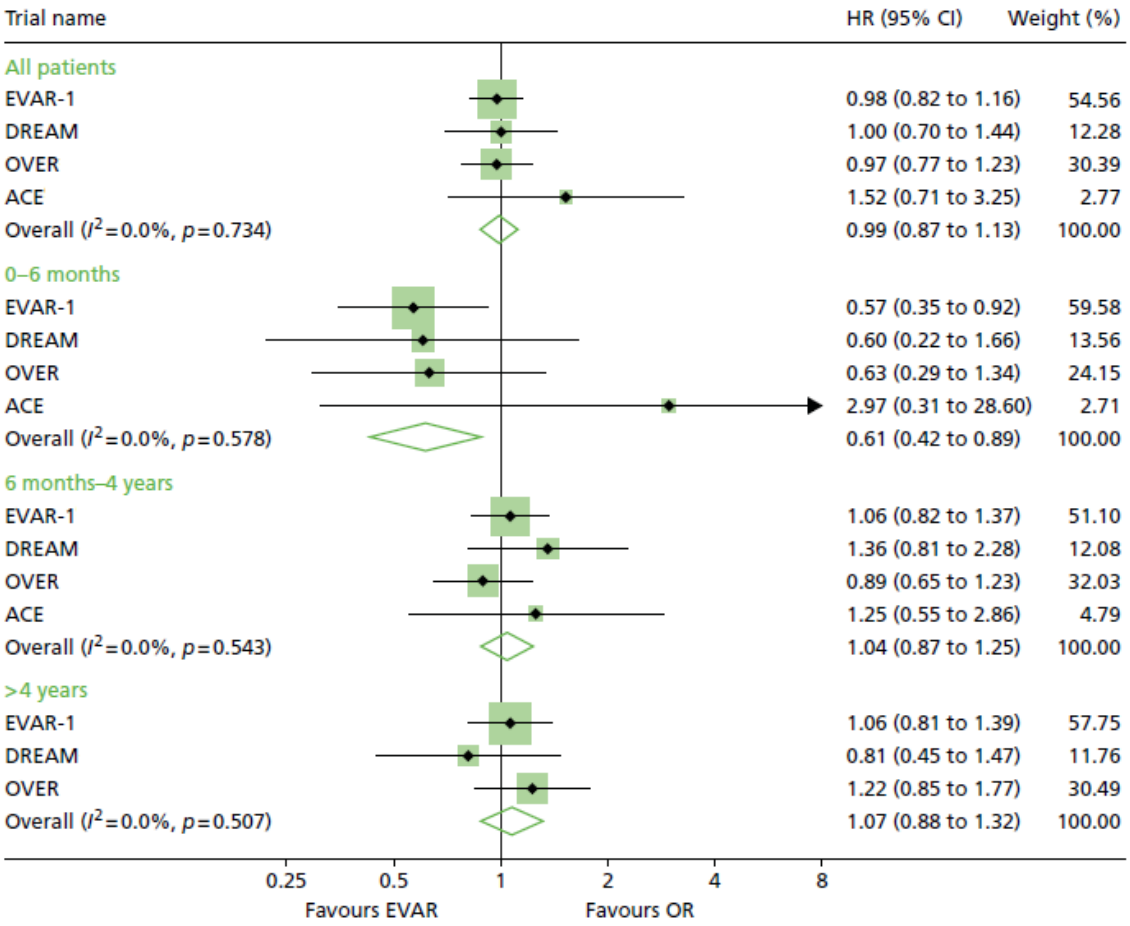
A) Main body of stent-graft, within its delivery system, has been introduced over a wire to the level of the renal arteries via the right and a contrast catheter has been placed via the left. B) The main body, with supra renal fixation is deployed sealing proximally in aorta and distally in right iliac artery. A wire has cannulated the short contralateral limb and a limb extension within its delivery system is position on the left. C)The left limb extension has been deployed completing the seal into the left iliac artery.
Credit: www.pngwave.com/png-clip-art-dabij

1.3.1 Evidence for EVAR

EVAR has been compared to OSR in 4 different randomised controlled trials (RCT).40-43 Survival at different times following randomisation, from an individual patient data meta-analysis of these 4 trials,44 demonstrates a statistically significant early, 0-6 months, advantage in survival in those who underwent EVAR but showed no survival advantage from 6 months – 4 years or > 4years follow-up, Figure 4 (page 9). The overall survival is equivalent between OSR and EVAR across the follow-up in the trials. A small percentage of EVARs fail to prevent aneurysm rupture, which has been recognised since the technique's inception. This was confirmed by a lower AAA specific survival rate after 15 years follow up in the UK EVAR 1 trial, EVAR had a 83% survival (95% CI 76-88% CI) vs OSR 88% (95% CI 78-95%), this did not reach statistical significance. [36 45]

EVAR intervention was compared to best medical therapy, in patients deemed unfit for OSR, in a single RCT – UK EVAR trial 2. It showed no difference in overall survival between the two groups.[46]

Figure 4: Survival Ratios Over Time from Meta-Analysis of 4 EVAR RCTs



Forrest Plot or 4 RCTS demonstrating no overall survival benefit of either EVAR or OSR, a small survival benefit exists for EVAR between 0- 6 months that is not sustained after 6month till >4years. (EVAR= Endovascular Aneurysm Repair, OSR= Open Surgical Repair).

Credit: DOI: 10.3310/hta22050 [36] Reproduced as per National Institute for Health Research permission

1.3.2 EVAR Complications and Secondary Interventions

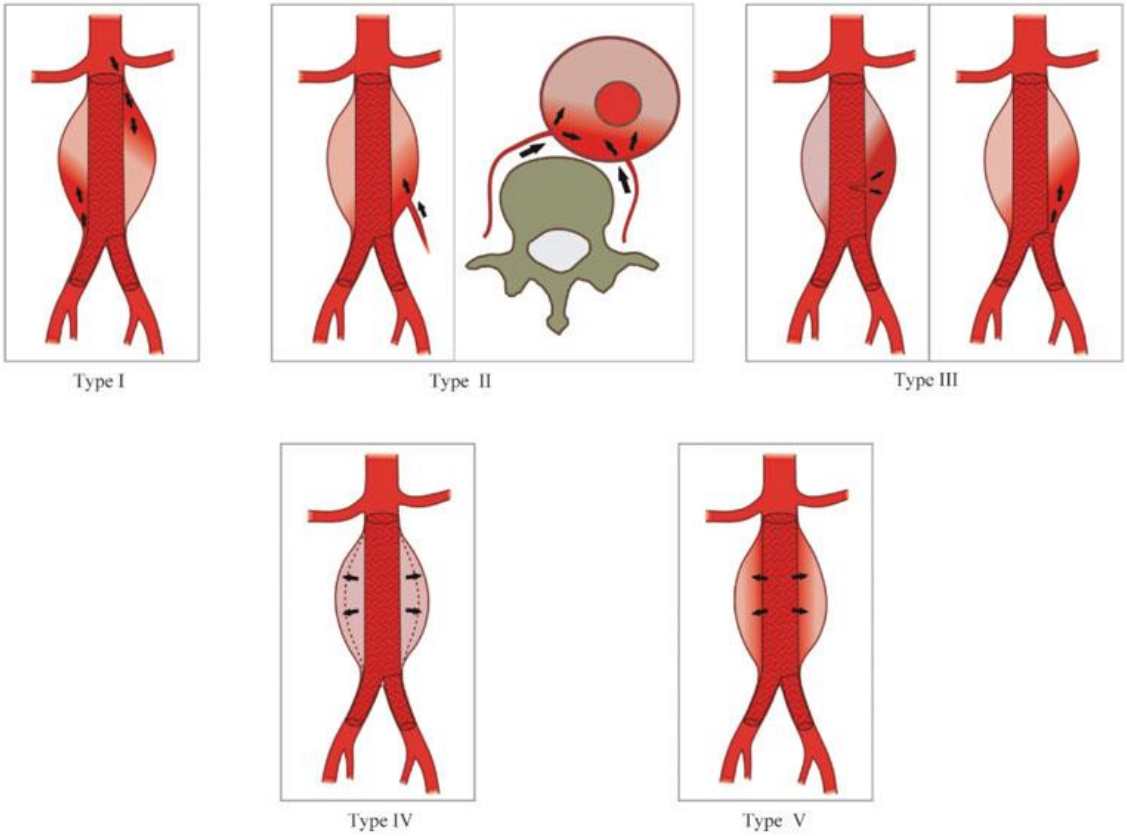
EVAR is associated with a higher rate of complications that require secondary interventions when compared with OSR, 16% vs 2.4% at 3 years.[41] These complications and secondary interventions to maintain treatment efficacy have been recognised since the inception of the technique and confirmed by EVARs secondary failure rate in observational studies as well as multiple RCTs.[40-43]

1.3.2.1 Endoleak

The commonest complication following EVAR is an endoleak,[47] endoleaks are blood flow outside the stent-graft but within the AAA. The accepted endoleaks classification is based on the source of blood flow into the AAA, Figure 5 (page 10).[48 49] In short endoleaks are classified as: type I is an ineffective seal of the stent-graft to native vessel

either proximally or distally; type II is blood flowing into the AAA from an aortic side branch; type III is due to a defect within or between different stent-graft components; type IV is due to porosity in the stent-graft fabric; and type V is AAA growth without a detectable endoleak.

Figure 5: Accepted Classification of Endoleaks Following EVAR



Endoleak Classificication: Type I-Flow into the aneurysm past the proximal or distal seal zone, Type II- Flow into the aneurysm from an aortic side branch, Type III- Flow into the aneurysm from a defect in or between stent-graft components, Type IV- Flow into the aneurysm by stent-graft material porosity (rather than defect), Type V- Growth of the aneurysm without evident flow.

Type IV endoleaks have rarely been reported since the first generation of EVAR stent-grafts as graft porosity has been addressed by manufacturers. Type V endoleaks are generally acknowledged to likely be an endoleak that is intermittent in nature or not detected on imaging. Endoleaks can therefore be grouped into stent-graft related (types I and III) and type II (non stent-graft related) endoleaks. Stent-graft related endoleaks generally transmit high pressure causing a high risk of aneurysm expansion/rupture (treatment failure).[51 52] The frequency of stent-graft related endoleaks is estimated to be 6-8% in the first 5 years following EVAR.[53] In contrast, type II endoleaks generally run

a benign course,[51 52] particularly in the absence of aneurysm expansion.[54] The frequency of type II endoleaks is estimated to be 20-40% in the first 5 years following EVAR.[53] Endoleak diagnosis involves two distinct components: detection of an endoleaks presence and characterisation/classification of that endoleak into a class or type of endoleak.

1.3.2.2 Stent-Graft Migration, Effacement and Component Separation

Type I endoleaks may occur due to: ineffective initial seal, disease progression in the native vessel or stent-graft movement, additionally components that combine to form an EVAR stent-graft can separate and lead to a type III endoleak. Given the risk of aneurysm rupture associated with stent-graft related endoleaks, the detection of impending failure is preferable to waiting for actual failure to occur. As such: movement of the stent-graft in relation to the vessel (migration), movement of components away from each other (component separation) and reduction in length of a sealing zone without migration (effacement) are often monitored to observe for impending failures.

Migration is typically defined as movement of the stent-graft of more than 5mm in relation to the vessel, it is typically distal movement at the proximal end of the stent-graft and proximal movement at the distal end of the stent-graft. 5mm was selected as it was twice the minimum interval (2.5mm) of axial imaging available on CT scans at the time of EVARs development, therefore guaranteeing true movement if diagnosed.[55] Stent-grafts have design features to help prevent migration these include: hooks or barbs, continual radial force and stent-grafts are designed to smooth sharp angulations. Barbs at the upper extent of the stent-graft penetrate the vessel wall so providing physical anchoring and resistance to distal migration. Stent-grafts are designed to expand to a larger size than the vessel into which they are placed providing radial force and a friction coefficient with the vessel wall so preventing migration. Finally stent graft design has evolved to allow them to conform around angulations in the AAAs morphology in a manner that reduces the ‘pull out’ force created.[56] The appropriateness of EVAR in individual AAA anatomical characteristics also influences the risk of migration. Individual stent-graft manufactures have Instruction For Use (IFU) for their products, based on their understanding of the stent-grafts performance in differing anatomical scenarios. This IFU details the manufacturers tolerances for safe anatomical limits for: minimum seal length (proximally and distally), AAA angulation and quality

of vessel at the seal zones, use of EVAR outside these IFUs is associated with higher rates of secondary intervention and adverse events.[57]

'Effacement' describes attenuation of seal zones from centrifugal enlargement of the arterial wall forming them and is commonly associated with AAA enlargement. As attenuation of seal zone occurs the reactive centripetal force applied by native aorta upon the stent-graft is proportionally reduced leading to stent-graft dilation or [partial] 'loss of constraint'. Proximal stent-graft dilation is observed for as a potential indicator of effacement but can occur without effacement present. The pathology of AAA formation is complex and while the vessels may macroscopically appear and be of normal diameter at seal zones the vessel is microscopically abnormal. Following EVAR the increases in proximal seal zone diameter have been measured as 2mm at 34 months and 5.3mm at 48 months,[58 59] the extent of dilation is associated with the extent of radial force applied by the stent-graft.[60] If sufficient dilation occurs the stent-graft will reach its maximum diameter thus preventing radial force, [total] 'loss of constraint', and loss of seal leads to a type I endoleak and pressurisation of the AAA with rupture risk. Migration and effacement often occur concurrently, this may occur as the applied radial force diminishes due to effacement and the closer a stent-graft gets to its maximum diameter reduces one of the forces resisting migration or migration may occur first reducing the length of seal meaning that less seal can be lost before significant effacement has occurred.

Stent-graft components typically rely on radial force of one component on another and the friction coefficient between the components to prevent them being pulled apart. AAA size following EVAR can increase or more often reduce significantly changing the AAA and therefore stent-graft morphology. This change in morphology, or indeed the original morphology, can mean the forces applied to the stent-graft result in separation of components. Separation of components leads to a type III endoleak and pressurisation of the AAA and associated rupture risk.

1.3.2.3 Limb Stenosis or Kinking and Occlusion

Flow through an EVAR stent-graft is imperative to perfuse the pelvis and lower limbs, loss of perfusion of a lower limb can ultimately lead to ischemia and amputation. The IMPROVE trial (an RCT comparing OSR and EVAR in ruptured AAA) included a patient group who unanimously ranked leg amputation as the most feared secondary intervention, ahead of even graft infection (Section 1.3.2.4, page 13).[61] Restriction of

flow through a stent-graft most commonly occurs within individual limbs and the point of restriction is referred to as a stenosis. A stenosis can occur as a result of; a narrowing processes within the lumen (thrombus formation or intimal hyperplasia), the limb itself taking a narrowed form (kinking) or from external compression of the limb (often one limb compressing another in a confined space). Limb occlusion is not rare with consistent reporting of 3-10% risk of suffering a limb occlusion following EVAR.[62 63] AAA size changes following EVAR change stent-graft morphology, the commonest clinical manifestation of these changes are lower limb symptoms as the result of impaired flow to the legs.

1.3.2.4 Infection and Other Complications

Stent-graft infection is a serious complication following EVAR, it can occur at any time following operation and is rare, with incidence reported at between 0.2 and 1%.[64 65] Curative treatment can only be achieved by surgical resection of the infected graft and anatomical or extra anatomical restoration of blood flow to the lower limbs and pelvis. The best reports of outcomes are case series, these demonstrate persistent infection following reconstruction in 25% of patients and a mortality of up to 60% in 5 years.[66] Many patients are not fit for or decline such surgery and as such are managed on antibiotic therapy with an expectation of ultimate palliation due to systemic infection or rupture of the aorta.

Aorto-enteric fistula (a connection between the aorta and bowel) are often associated with stent-graft infection but can also occur independently in approximately 0.5% of EVAR cases.[53] Surgical repair is complex as it involves enteric repair or diversion in addition to stent-graft resection and is often required in patients with active bleeding and/or shock. As such endovascular occlusion of the inflow to the fistula is often used as a bridge to stabilise the patient and perform excision of grafts on a planned basis.[67]

1.3.3 Rationale, Aims and Evidence for Surveillance

Owing to the risk of complications following EVAR, surveillance imaging is mandated following EVAR.[17 68] The requirement for enrolling patients in post-EVAR surveillance is almost ubiquitous among practitioners undertaking EVAR. Surveillances' value is further highlighted by the results of 15-year follow-up after EVAR in the landmark RCT,[45] which showed higher late aneurysm related mortalities in the EVAR arm compared to OSR arm which is suggestive of treatment failure. Surveillance involves diagnostic tests and its objectives are similar to that of population screening. The World

Health Organisations criteria for an effective screening programme offer a helpful framework for highlighting areas for improvement.[69] EVAR surveillance should detect conditions that are better treated earlier than later and have effective interventions for those conditions. It should also have an agreed test and definitions for diagnosis of the condition.

No RCT regarding the efficacy (detection and treatment of surveillance findings) of surveillance has been, or is ever likely to be, undertaken. Two sizeable studies have attempted to assess the efficacy of EVAR surveillance using national administrative databases. The first study by Garg et al. looked at 9,503 Medicare patients who underwent EVAR between 2002 and 2005 and binarily categorised them as receiving complete or incomplete surveillance (as defined by [American] Society for Vascular Surgery).[70] 43% of patients were compliant, the two groups were then propensity matched for patient demographics, treating hospital volume and patient co-morbidities. The groups outcomes were then compared at the end of the follow-up period. They showed, with a mean follow-up of 5.2 years, that patients in the incomplete surveillance group experienced lower rates of total complications (2.1% vs 14.0%; $p < 0.001$), late rupture (1.1%vs 5.3%; $p < 0.001$), major or minor reinterventions (1.4%vs 10.0%; $p < 0.001$), aneurysm-related mortality (0.4%vs 1.3%; $p < .001$), and all-cause mortality (30.9%vs 68.8%, $p < 0.001$).

The second study by de Mastral et al. used health databases in Ontario, Canada, to identify 4988 patients who underwent EVAR between 2004 and 2014.[71] They defined compliance with surveillance as a CT scan or ultrasound of the abdomen within 90 days of EVAR as well as every 15 months thereafter, available confounding variables were then adjusted for. Consistent compliance was associated with a lower risk of death when compared with missing the first imaging follow-up within 90 days (HR 0.82, 95% CI 0.69-0.96, $p = 0.014$), or when compared with having first imaging follow-up within 90 days but subsequently not compliant (HR 0.78, 95% CI 0.68-0.91, $p < 0.001$). While only 58% of patients met these criteria over the entirety of their follow-up, de Mastral et al. looked at the proportion of follow-up time compliant and the higher the proportion of time the lower the risk of death (HR 0.87, 95% CI 0.79-0.96, $p =0.019$) per 25% increment in time compliant at 10 years of follow-up.

There is therefore disagreement in the literature regarding the efficacy of EVAR surveillance, likely as the result of the studies differing methodology. Garg et al's study retrospectively assigns a binary attribute of compliant or non-compliant to each patients

entire follow-up regardless of timing of non-compliance and then assesses events throughout follow-up to those end of follow-up categories. This means events that occurred prior to non-compliance are attributed to a yet to occur variable. The reason for ultimate non-compliance is an obvious unknown confounder which can / is not be compensated for in that study. de Mastral et al similarly performed a binary whole follow-up analysis but also looked at each segment of follow-up and eloquently demonstrates increasing time compliant with surveillance was associated with a lower risk of death, this analysis reduces the importance the reason for non-compliance confounder, as non-compliance is changed to a ordinal rather than binary variable. As such the Ontario study is likely a superior study to base prospective decision on future patents care but both studies are limited by not knowing the reasons for patient non-compliance (57 and 42% respectively) due to the data sources.

The imaging modalities described for EVAR surveillance are discussed below.

1.3.4 Computer Tomography +/- Angiography

Computer Tomography (CT) was invented by Godfrey Hounsfield and synchronously by Allan Cormack in 1972. It uses digital processing to generate a three-dimensional (3D) volume of the inside of the patient from a series of two-dimensional radiographic (x-ray) exposures taken around a single axis of rotation, termed a slice. This is repeated in series, along the required length of the patient, thereby generating a 3D volume of the extent required. The granularity of the volume depends on both the size and number of radiographic exposures per a rotation and the increment of length between the rotations. Each 3D unit of granularity in the construction is termed a voxel and is encoded with the average density of its contents, this is on the Hounsfield scale which runs from +3,071 (most dense) to −1,024 (least dense). The X-rays used in the radiographic exposure are a form of electromagnetic radiation, the number of X-rays and energy with which they are expelled from the machine can be varied. The higher the energy, measured in Electron kinetic energy (keV), an X-ray has the denser the material it can pass through to reach the detector and the larger the number of X-rays used, measured in milliamperes (mA) the greater the resolution of densities that can be measured. Effectively keV determines the range of densities that can be delineated and mA determines the increments of different densities that can be delineated.

This volume is reviewed as an image in one plane or multi-planar reconstruction (MPR)

to make a diagnosis and can even be rendered into a 3D reconstruction to aid understanding.

The administration of iodinated intravenous contrast and then acquisition of the CT volume when that contrast has reached the arterial or venous circulation in the anatomy of interest is termed Computer Tomography Angiography (CTA). This adds an additional variable as it requires the timing of the CT volumes acquisition to coincide with the contrast passing through the vascular anatomy of interest. The delay between intravenous injection and contrast arrival is dependent on a large number of patient and administration variables. CTA is used to delineate blood and perfused tissues from other surrounding body tissues that may have very similar densities but no perfusion. This is imperative in EVAR surveillance as blood and thrombus have very similar densities and differentiating graft occlusions and endoleaks (which typically run in AAAs filled with thrombus) are key diagnostic criteria. It is also possible to perform multiple CT's or phases following the administration of a single dose of contrast to view the anatomy at various states of perfusion.

Concerns regarding the use of CTA in EVAR surveillance relate to the cost, use of the potentially nephrotoxic contrast agents and the repeated radiation exposure potentially leading to increased rates of neoplasm.[45] CTA is often referred to as the 'Gold Standard' of EVAR surveillance, this is predominantly due to it being the non-invasive modality of surveillance used from the inception of the technique.[39] Modern CTA has never been compared to a theoretically superior comparative standard for detecting endoleaks ([invasive] catheter directed digital subtraction angiography could be used) therefore its own sensitivity and specificity are unknown, despite this it is often used as the comparative standard for other modalities.[72] There is not a published consensus of: optimum CT settings, contrast type, contrast volume, delay of acquisition or even number of phases that should be used for CTA in EVAR surveillance. The technology of CTA has advanced in every definition of imaging quality, since the time EVAR was first used, despite this almost all comparative studies between EVAR surveillance imaging modalities use the term CTA for every generation of the technology ubiquitously. Individual studies reporting diagnostic accuracy of CTA to detect various complications of EVAR rarely report adequate detail of the CTA settings used to allow duplication of that version in clinical practice and subsequent meta-analysis of these results simply group all CTA's together regardless of even the number of phases acquired.[72 73]

Regarding endoleak detection CTA has been compared to Colour Duplex Ultrasound Scans (CDUS) and Contrast Enhanced Ultrasound (CUES) in multiple studies and these have been in turn subjected to multiple meta-analyses.[72 73] All but one, assume CTA to be the 'Gold standard', the result of which are reported below, section 1.3.6 (page 19) and 1.3.7 (page 21) respectively. Karthikesalingam et al. conducted a secondary analysis inverting the above assumption, testing that CEUS was in fact superior to CTA and found "CTA would have low pooled sensitivity of 0.70 (95%CI 0.53 – 0.82) but high pooled specificity of 0.98 (95%CI 0.94 – 1.00) in relation to CEUS".[73] Few of the included studies offer sufficient detail of the CTA protocols to allow replication.

With regard stent-graft migration and effacement CTA is unchallenged as the gold standard in diagnosis and quantification of both. The use of contrast and MPR allow clear and detailed interrogation of the stent-graft and native arterial wall to allow quantification of both migration and/or effacement. No other imaging modality allows as detailed interrogation of both of these elements. Standardised Abdominal Radiography (AXR) allows comparison of stent-graft position to bony landmarks, surrogate as reference points, to assess for migration. Optimum CTA settings to detect migration and or effacement have not been investigated. Component separation is likely best detected on a radiographic image,[74] similar images can be reconstructed from a CT volume but can equally be acquired separately and with a lower radiation exposure.

Stenosis or reduction in the size of a flow channel cross section can be delineated and quantified on CTA. Limb stenosis or kinking can therefore be diagnosed on CTA, however looking at the flow lumen at each point along its length is time consuming and unlikely to be completed routinely in clinical practice. It is more common practice for gross abnormalities to be noticed during other interrogation of the CTA and then selectively reported.

Infection of an aortic graft is defined by the "The Management of Aortic Graft Infection Collaboration" (MAGIC) criteria,[75] the major imaging criteria are all CT based and therefore the only [routine] imaging technique that can definitively contribute to this diagnosis is CT. The substantially more expensive and less available fluorodeoxyglucose positron emission computer tomography may have a confirmatory role but is not an appropriate initial test.[53]

1.3.5 Plain Abdominal Radiography (X-Ray)

Plain Abdominal Radiography (AXR) is acquired by placing the patient between a source of X-rays and a detector plate, the source emits X-rays in single plane over a defined area and the length of the exposure can also be varied to increase penetration of X-rays through to the detector. As AXR are taken by placing the patient between a source of X-rays and a detector changes in the orientation and distances of the these can lead to variation in geometry that can distort the apparent position of the stent-graft relative to bony landmarks on the resulting AXR.[76] A standard set of AXR acquisition settings and patient position was developed to minimise these effects, the Liverpool – Perth protocol.[74]

AXR with anteroposterior and lateral projections has been used during EVAR surveillance for detection of component separation, effacement and migration.[77] This was initially due to CT not having an adequate resolution to definitively define all the required components of the stent-grafts to allow for diagnosis,[74] and more recently has been to allow detection of these complications without routine use of CT.[78] AXR has a significantly lower radiation exposure than CT and does not suffer from metallic coil–related artefact as Magnetic Resonance Angiogram (MRA) does, it is also a fraction of the cost of cross-sectional modalities such as CTA and MRA. AXR is not an adequate EVAR surveillance imaging modality in isolation as it is unable to measure AAA size or detect endoleaks.

Migration is detected on AXR by comparing stent-graft position (and angulation) in relation to bone landmarks on serial images. Baseline images taken shortly after implantation or at the same time as a CTA allow changes compared to bony landmarks to be inferred as movements in comparison to the arterial vessel wall. Potential effacement is suspected and can be further investigated when serial comparison of stent-graft appearance at the seal zone demonstrates dilation or changes in morphology of the stent that lies within the seal zone. Stent-graft component separation is detected by comparing relative positions of stent-graft components in serial images. Each stent-graft component have radio opaque markers used at the time of insertion that aid this detection.

Stent graft distortion, in the form of kinking of the metallic structure of the composite stent-graft, can be diagnosed on single AXRs and evolution of this can be described over serial images. AXR cannot however reveal what is happening to the flow through the corresponding lumen which is radiopaque on AXR. In the literature migration is the

most described complication detected on AXR,[78] and normally prompts a CTA to be performed to confirm and quantify the extent of migration as well as plan any secondary intervention that is required.

1.3.6 Ultrasound and Colour Duplex Ultrasound Scan

Medical ultrasound scans use soundwaves with frequencies up to 20,000 Hz to form images of tissues within the body. The simplest form of these is B-mode (brightness), this forms a single planar greyscale image of the tissues. This is formed by the ultrasound probe, while in contact with the body surface, emitting a series of pulses of sound waves and recording the reflected echoes of these pulses. Differing tissues have differing reflective properties and as such tissues can be differentiated by intensity of reflections. Fluid has very low reflective properties (appearing black on images) while solid objects typically have very high reflective properties appearing white on images. Varying the frequency and amplitude (gain) of sound used as well as the depth of focus and shape of probe (changes the shape of the array of sound emitted) can be used to increase the range of body areas that can be imaged. Ultrasound waves must be able to conduct through the tissue to be able to form images, structures that have high impedance and cannot conduct sound waves of these frequencies (typically air) simple fail to conduct waves and create a "shadow" or missing element of the resultant images.

3D ultrasound can be created by sweeping the probe over a portion of the body then using post processing it is possible to combine this series of 2D images into a 3D reconstruction. This is rarely used in clinical EVAR surveillance. B-Mode ultrasound can be used to interrogate the AAA size in EVAR surveillance and morphology of the aneurysm and outflow. Proximal (neck) imaging can be hindered by air in the first part of small bowel (duodenum) and similarly colonic gas can hinder views of the iliac (outflow) vessels – this is almost guaranteed if the patient has a stoma which typically overlies iliac vessels.

Colour Duplex Ultrasound Scan (CDUS), combines B-Mode ultrasound with intermittent use of two forms of Doppler imaging. This imaging relies of the principles of Doppler shift described by Christian Doppler in 1842, he observed that when a wave is reflected (or emitted) by an object that is itself moving it increased the frequency of that wave. The reverse is also true, objects moving away reflect waves with a lower frequency. Ultrasound machines can delineate the frequency of the reflected waves and can present this information in various ways and display it on or with the B-Mode

image. Colour [Doppler] Mode Ultrasound scans present a B-Mode ultrasound with a colour overlay to delineate any movement within the image displayed. The sensitivity to movement and range of velocities displayed can be varied by the ultrasound operator. In EVAR surveillance this allows the presence of blood flow to be confirmed so can demonstrate the patency of stent-grafts and limbs, it can also demonstrate flow outside the stent-graft but within the AAA therefore detecting an endoleak. Skilled operators in favourable patients can trace endoleak flow to its origin and therefore characterise endoleak type using Colour Mode Ultrasound. Similarly, skilled operators can demonstrate turbulent flow suggestive of stenosis within the stent-graft lumen using colour mode. Duplex Ultrasound typically refers to the use of B-mode ultrasound and pulsed wave Doppler on the same image. Pulsed wave Doppler presents velocity information sampled from a small area of a B-Mode image and presents that information on a timeline allowing quantification of the velocities observed over several cardiac cycles. Fluid under a consistent pressure will flow more rapidly in a vessel that becomes narrowed, therefore allowing quantification of the extent of the narrowing. Within EVAR surveillance Duplex Ultrasound is therefore used to determine directionality of flow in endoleaks (helping to delineate types) and to quantify the extent of stenosis in the stent-graft flow lumen.
B-Mode, Colour Mode and Duplex Ultrasound are all used at a variety of times in a single scan in the majority of EVAR surveillance performed by ultrasound as such "Colour Duplex Ultrasound Scan" - CDUS is the most appropriate term. The skill in selecting the optimum ultrasound settings, mode and obtaining quality images or measurements in the setting of EVAR surveillance results in inter-operator variability.

CDUS offers "repeated and reliable measurement of maximum aneurysm diameter at low cost",[53] however the measurements taken on CDUS are not directly comparable to CTA and the 95% confidence interval for difference in measurements is less than 10.6mm.[79] These serial measurements of size allow diagnosis of type IV or occult endoleaks and type II endoleaks to be stratified into low risk and high risk endoleaks, based on growth or stasis/decay of aneurysm size.[54] Graft-related endoleaks are often associated with size increases but should be further investigated/treated even in the absence of changes in size, as they may have only recently developed.

On meta-analysis, using (undefined) CTA as the comparator standard, CDUS can detect any endoleak with a sensitivity of 0.82 (95%CI 0.66 – 0.91) and a specificity of 0.93 (0.87 – 0.96).[72] CDUS is similarly successful in detecting and differentiating graft-

related endoleaks, with a sensitivity of 0.83 (0.40 – 0.97) and specificity of 1.00 (0.97 – 1.00).[73] Both of these meta-analyses are however based almost exclusively on the same cohort of retrospective observational studies, these have a risk of bias due to a lack of blinding particularly with respect to characterisation of endoleak type. The meta-analyses themselves are equally flawed in that they don't account for differences in technique or protocol in acquisition of CDUS and CTA and the use CTA as a gold standard when it is itself has unknown diagnostic ability is questionable.

CDUS examination of limb stenosis and subsequent rates of occlusion or secondary interventions are sparse in the literature. This is in part due to the subjective nature of screening using B-Mode and Colour Doppler ultrasound that are relatively poorly described. There is some evidence that duplex measurements at the distal seal zones in the iliac arteries can predict limb occlusions or secondary interventions. A retrospective review of measurements in an EVAR surveillance programme showed that a peak systolic velocity (taken as part of duplex measurements) >300m/s had a sensitivity of 100% and a specificity of 98% for suffering a limb occlusion.[63] This system to differentiate patients has not been validated in another centre or been tested for inter/intra observer variability.

1.3.7 Contrast Enhanced Ultrasound Scan

Agents introduced into the bloodstream that have high sonic reflective qualities have long been recognised to better delineate blood flow on ultrasound. Gramiak et al. described the first use of this in medical imaging in 1969, using non-specific contrast agents that had such short half-lives in the blood stream that they required catheters to facilitate direct injection into the heart for contrast echocardiography.[80] The lack of a stable contrast agent, that could therefore be injected intravenously, prevented the wide spread use of Contrast Enhanced Ultrasound (CEUS) until the 1990's. Since the availability of the first stable contrast agent an increasing variety of applications for CEUS have been found, including EVAR surveillance. All commercially available ultrasound contrast agents now consist of microbubbles with a diameter <10µm and constitute a shell with a gaseous interior that have half-lives long enough to allow intravenous injection and meaningful ultrasound interrogation in the patient's tissue. Microbubbles are commonly made of lipid shells which the body ultimately metabolises, and a gas centre that is expired by the respiratory system following bubble

rupture. Microbubble contrasts are remarkably safe with adverse event rates as low as 0.020%.[81]

CEUS initially relied purely upon the high reflective properties of contrast agents, that were the result of the acoustic-impedance mismatch between blood and the gas contained within the microbubbles. This was visualised in B-Mode or Colour [Doppler] mode as increased signal making blood flow easier to delineate, in comparison to surrounding tissues. This method did however still require the operator to interpret high intensity on the image was the result of contrast agent and not highly reflective tissues. CEUS imaging was refined further when the phenomenon of Harmonic Imaging (HI) and later Pulse or Phase Inversion Imaging (PII) were implemented, HI and PII are collectively referred to as Coherent contrast imaging. Coherent contrast imaging is a technological solution which uses HI or PII techniques that both rely of the physics of the ultrasound waves interaction with microbubble contrast agents to allow the operator to observe increased delineation of microbubbles on the ultrasound image.

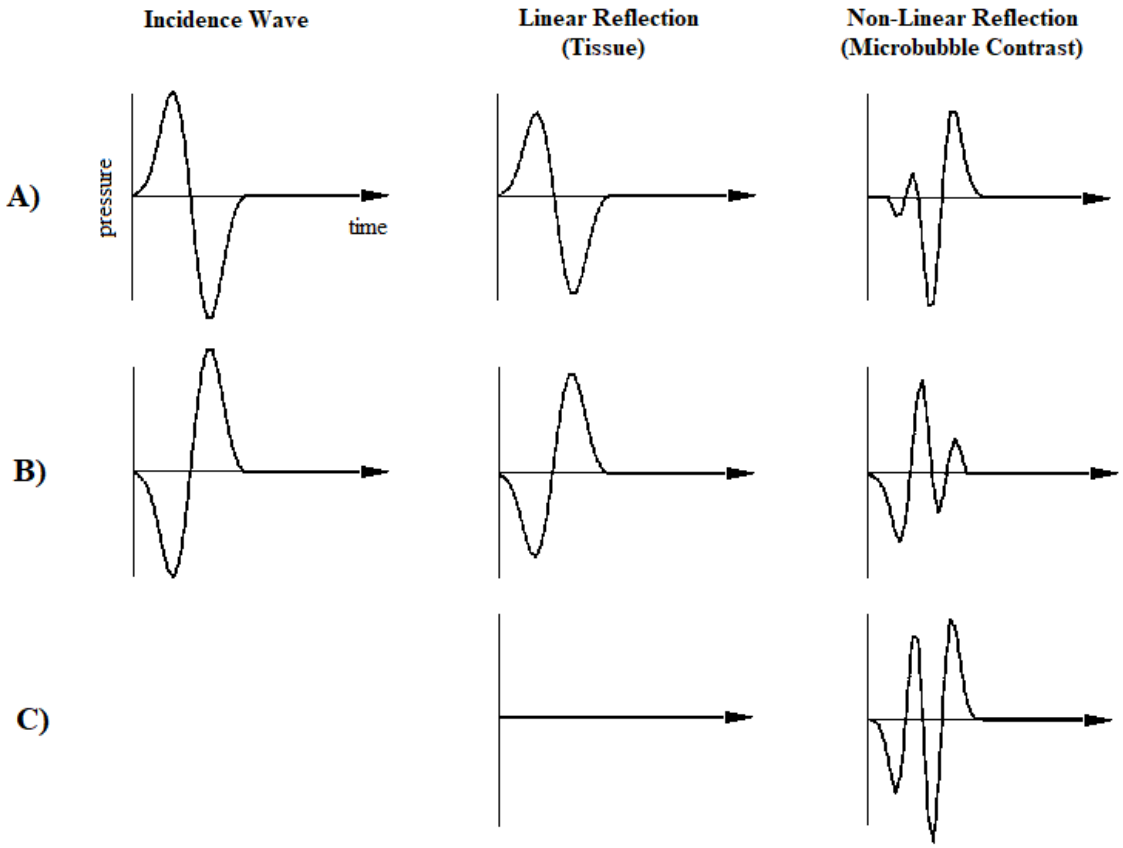
Spherical microbubbles are compressed when subjected to high pressure elements of sound waves, but eventually can compress no further and reflect the remaining element of the positive pressure. As the pressure decreases the bubbles expands and releases this stored energy creating an over expansion of the bubble in the low-pressure phase of the wave leading to a second positive pressure wave. This means for each incident wave the bubble reflects two complete (lower energy) waves – a doubling of frequency. This phenomenon is termed non-linear reflection, the resultant wave forms are demonstrated in section A of Figure 6 (page 23). Other tissues in the body can, to a much lesser degree, also create this phenomenon but typically return a linear reflection, by optimising the emitted wave characteristics and adjusting the ultrasound machine settings it is possible to significantly improve delineation of the contrast from tissue and therefore delineation of blood flow from surrounding tissues. Essentially the level of opacification of any part of the image on the ultrasound screen is no longer a function of just amplitude of the reflected wave but of the frequency and amplitude of the reflected wave. The microbubbles expand and contract to each wave they are exposed to, so microscopically look to be vibrating, hence the term Harmonic Imaging.

PII sends two ultrasound pulses of inverse waveforms, in quick succession. Linear reflection waves are therefore also directly mirrored, while non-linear reflections are manifestly not, section A and B of Figure 6 (page 23). In PII the two reflected waveforms are added (summed) upon receipt and displayed, linear/tissue reflections

cancel each other out leading to no signal displayed on screen while non-linear reflections are asymmetrical and do not cancel each other out leading to high signal being displayed, section C of Figure 6 (page 23). This leads to much better delineation of the contrast agents from surrounding tissues than HI. PII is often displayed as a split screen, half the screen displays only the standard incidence wave response (B-mode ultrasound) while the other displays the sum of the incidence and inverse incidence waves response (PII). This split screen allows B-Mode to be used to delineate anatomy and positioning while the PII demonstrates the contrast enhancement, Figure 7 (page 24).

One study has been undertaken regarding the optimum quantity of microbubble contrast agents required in Coherent Contrast Imaging within EVAR surveillance, it used HI and found that 2.4mls was superior to 1.2mls, of second generation microbubble contrast agent, in visual delineation of endoleaks.[82]

Figure 6: Waveforms in Coherent Contrast Ultrasound Imaging

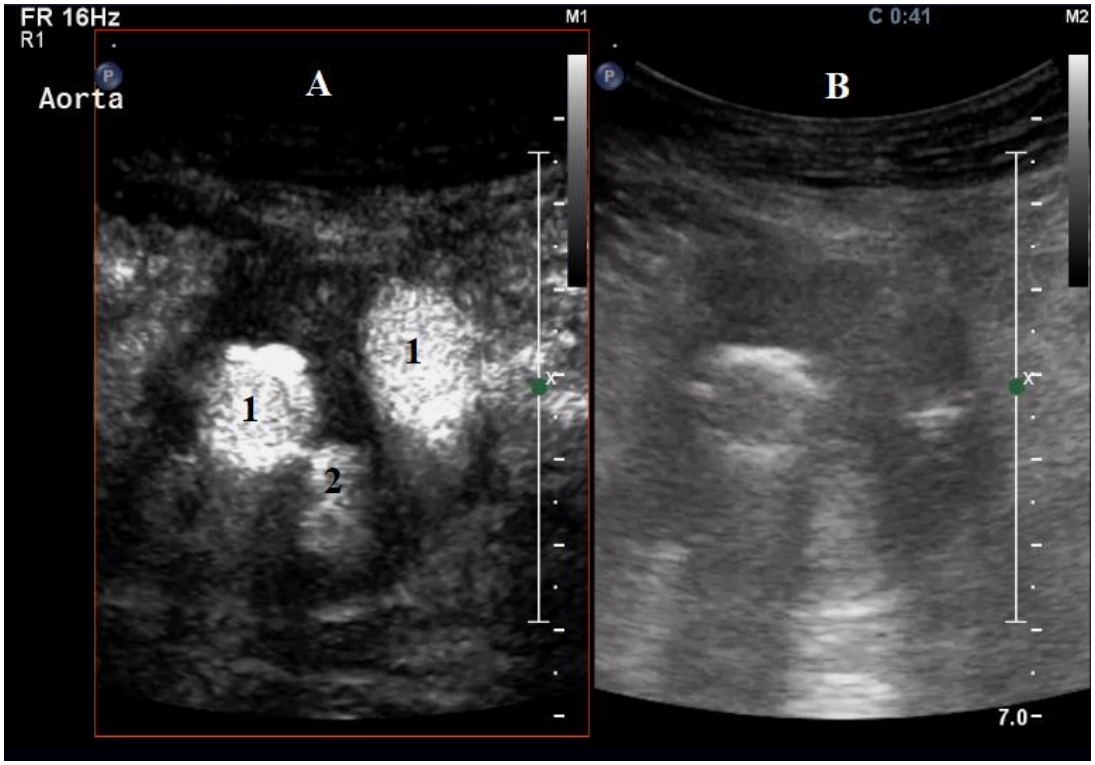


A) Incident and reflected waveforms demonstrating linear and non-linear waveforms used in Harmonic Imaging, **B)** Inverse **i**ncident and reflected waveforms of A, **C)** Sum of (A and B) reflected waveforms used in Phase Inversion Imaging

CEUS can be used for endoleak detection and characterisation in EVAR surveillance, it is typically combined with CDUS as an adjunct that is perceived to increase endoleak detection. CEUS is not known to improve any of the other EVAR surveillance attributes of CDUS. As described above, CEUS is a global term for 3 technological solutions that have incrementally increased detection/delineation of contrast and therefore endoleaks over the 2 decades that it has been used in EVAR. Despite this the description of the CEUS technique and contrast agent / quantity used are poorly described in individual studies and often universally combined for evidence synthesis and comparison by meta-analysis.

Similarly to CDUS, meta-analysis of CEUS endoleak detection and characterisations is based on studies that often use undefined CTA as the comparator standard, CEUS can detect any endoleak with a sensitivity of 0.94 (95%CI 0.85 – 0.98) and a specificity of 0.95 (0.90 – 0.98).[72] CEUS is reported as highly successful in detecting and differentiating graft-related endoleaks, with a sensitivity of 0.99 (0.25 – 1.00) and specificity of 1.00 (0.98 – 1.00).[73] These primary studies and meta-analyses share the same methodological flaw as the analyses for CDUS.

Figure 7: Ultrasound Display from Contrast Enhanced Ultrasound Using Phase Inversion Imaging



CEUS using PII: **A)** Phase Inversion Image, **B)** B-Mode Ultrasound Image, **1)** EVAR limbs -containing microbubble contrast, **2)** Type III Endoleak arsing from side of EVAR limb.

1.4 Surveillance Regimens Following EVAR

Parodi et al. followed their initial cases of EVAR with CTA and CDUS, initially to confirm the treatment's efficacy but quickly recognised the potential complications and need for continued surveillance.[39] As EVAR technology evolved, the need for surveillance was maintained[49] and remains recommended to this day.[53 83] The manufacturers of the commonest EVAR stent-grafts used in the UK still suggest use of AXR and CTA,[84-86] suggesting at least annual intervals,[84] or up to 4 imaging visits in the first year before then reducing intensity to simple annual follow-up.[85 86] The European Society for Vascular Surgery suggest that a combination of CTA and/or CDUS can be used in differing combinations and intensities depending on patient risk, with up to 5 years between surveillance visits for low risk patients.[53] The [American] Society for Vascular Surgery recommend a combination of CTA and CDUS at differing intensities dependent on patient risk with at most 1 year between surveillance visits.[83] Actual UK practice in 41 centres in 2011 was similarly varied with centres differing in their primary imaging modality (CTA or CDUS or CTA and CDUS) and AXR was used as an adjunct in a minority of centres only.[87] Practice had evolved by 2019 when 6 out of 10 UK centres used AXR routinely and all used a combination of both CTA and CDUS, with less frequent CTA in the first 5 years following EVAR.[88]

There are no randomised trials comparing regimens of either imaging modalities or intensity of EVAR surveillance. Most published evidence is either the comparison of cohorts between different centres,[88] or different regimens at different time within the same centre.[78] All of these cohort studies suffer from significant confounding as a result of differences in practice, experience and stent-graft use that occur over time and between centres. As such most surveillance regimens are derived from expert opinion.[17 83] These typically base decisions on the most appropriate imaging modality around their perceived accuracy as well as cost and risks. Some regimens also stratify the risk of individual patients based upon certain characteristics.[53]

Risk stratifying patients for EVAR surveillance has been attempted several times but there are two notable systems. The St George's Vascular Institute score uses pre-operative aneurysm size data to predict post EVAR risk of requiring secondary intervention, it has been extensively validated both within the UK and internationally.[89 90] Even in the initial paper this method had a secondary intervention rate of 12% in the low risk group by 5 years, this is likely the result of being unable to account for the quality of the repair performed. Bastos et al. categorised patients as low risk (proximal

and distal sealing zone at least 10 mm and no endoleak) or high risk (sealing zone less than 10 mm proximally or distally and/or presence of any endoleak) on the first CTA following EVAR.[91] On a validation study the low risk group had a secondary intervention rate of 7% by 5 years, however there were only 129 patients at risk by this time which will give this prediction wide confidence intervals.[92] Neither the original or validation study publish their CTA acquisition protocol to allow replication in real world clinical practice, despite this they form the basis on which The European Society for Vascular Surgery guidelines suggest stratifying surveillance intensity.[53]

1.5 Summary

Post-EVAR surveillance has been standard practice since introduction of EVAR. Although initially proposed only because of uncertainties regarding the new treatment, surveillance soon revealed a variety of complications occurring throughout follow-up into the long term. Modes and mechanisms through which these complications occur, and cause treatment failure have been described along with their relative significance. Improvements in stent-graft technology and physician understanding of how to best utilise EVAR technology have likely resulted in a reduction but not elimination of these complications. Surveillance remains essential to identify these complications so that remedial secondary interventions might be undertaken before failure of treatment occurs. However, the evidence-base to guide best practice regarding surveillance remains insufficient.

Several imaging modalities are in use for surveillance with AXR, CDUS, CEUS and CTA being the main modalities. Each of these modalities has its unique advantages and disadvantages but all are vulnerable to variations in diagnostic accuracy due to variations in acquisition and reporting standards. Imaging reports comprise observation relating to numerous aspects of stent-graft and vascular anatomy but relative importance of these remains undetermined. Almost universally, surveillance imaging is offered to all patients at same intervals despite a recognition that individual risk varies, sometimes markedly so, leading to wasted imaging in some patients while others present with failure of treatment between surveillance intervals. Personalised surveillance based on findings readily detectable on standard imaging modalities at each point of follow-up has the potential to render surveillance clinically more effective as well as potentially cheaper and more tolerable to patients. Patient compliance with surveillance is poor in

many centres due to poorly understood causes and improving compliance is essential for a surveillance programme to be effective.

1.6 Hypotheses and Aims

1.6.1 Incidence and Indication for Secondary Intervention

Current published literature on secondary interventions following EVAR reports either "Freedom from [First] Secondary Intervention" or "[mean] Incidence of Secondary Interventions" as well as the types of secondary intervention over the period of follow-up in that study. These outcome measures offer pre-operative information for patients as to their risk of requiring any secondary intervention and data for health economic calculations respectively, but do not offer enough granularity of information to help inform surveillance regimen design.

Hypothesis:

The incidence of, and indication for secondary interventions varies over time following EVAR

Aim:

Describe the indication and incidence of secondary interventions at different time points following EVAR

1.6.2 Rate of Compliance with EVAR Surveillance

Compliance with EVAR surveillance is variable but generally reported to be poor, it is also typically reported as a binary state for each patient across the entire follow-up period studied. An individual patients' compliance can vary over time and therefore a single binary measurement of compliance may be misleading depending on the timing of the measurement.

Hypothesis:

Overall compliance rates with EVAR surveillance vary over time following EVAR

Aim:

Describe the rate of compliance with EVAR surveillance at different time points following EVAR

1.6.3 Factors Associated with EVAR Compliance

Multiple patient related factors have been shown to be associated with decreased EVAR surveillance compliance, but no study has adequately examined the interactions between these associations - to assess for confounding between factors. A study in a centre with good compliance, therefore removing system-based factors as a further confounder, could highlight the best targets for patient-based research to improve compliance.

Hypothesis:

There is a high degree of confounding between the factors considered to be associated with poor EVAR compliance

Aim:

Describe the level of association between the proposed factors and EVAR surveillance compliance, adjusted for co-linearity / confounding between variables.

1.6.4 Findings on CDUS and AXR

CDUS with AXR are the most common EVAR surveillance imaging modalities used in the UK. While there have been multiple diagnostic imaging studies labelled with these overarching technologies, little is known about which specific findings available on CDUS and AXR are associated with secondary interventions and if in fact the number of findings recorded could be reduced.

Hypothesis:

Different findings available on CDUS and AXR have different levels of association with subsequent secondary interventions and reducing the total number of findings collected can be achieved without reducing the overall association.

Aim:

Describe the level of association of individual findings available on CDUS and AXR and assess the impact of reducing the number of findings recorded on association with subsequent secondary interventions.

1.6.5 Secondary Intervention Risk Prediction

Current proposals to rationalise EVAR surveillance, by stratifying patient risk, all rely on single peri-operative snapshots to risk stratify patients into high or low risk groups. This means predictions have large confidence intervals after a few years and large patient numbers are required to generate accurate predictions. Such a system also

naturally has a limited ability to improve surveillance programme efficiency. A model that can be used at any time after EVAR and predict future risk, could vary intervals of surveillance directly proportional to the patients' risk, which offers high efficiencies with greater predictive accuracy as patients feed into the model at multiple time points.

Hypothesis:
It is possible to accurately predict the risk of secondary intervention at multiple time points during EVAR surveillance.

Aim:
To create a risk prediction model that can accurately predict future risk of requiring a secondary intervention based on variables readily accessible on a routine surveillance visit.

1.6.6 CEUS Endoleak Detection Rate

Current literature does not adequately describe the CTA and CEUS protocols used to allow replication in clinical practice. As such it is not clear if CEUS has an equivalent ability to diagnose endoleaks as CTA. The cost of CEUS means that it likely needs to be equivocal or superior to CTA to form part of a routine ultrasound-based surveillance programme. A high-quality prospective study comparing endoleak diagnosis on CEUS compared to a well-defined, reproducible, CTA standard is required.

Hypothesis:
CEUS is near equivalent to CTA in graft-related endoleak diagnosis.

Aim:
Compare CEUS to a well-defined, optimised form of CTA in endoleak diagnosis and compare these to a "Gold standard" of final diagnosis.

1.6.7 CTA phase Optimisation

The number and timing of CTA phases in EVAR surveillance is poorly described and with little scientific basis. A more scientific approach to their design requires an understanding of the timing of endoleak opacification on CTA.

Hypothesis:
Endoleak opacification on CTA differs by endoleak type.

Aim:
Describe the timing of opacification of different endoleaks on CTA.

2 Analysis of a Colour Duplex Ultrasound Scan and Plain Abdominal X-ray Surveillance Regimen

Surveillance following Endovascular Aneurysm Repair (EVAR) was initially empirically designed by pioneers of the technique. It remains mandated, in various forms, by nearly all practitioners who undertake EVAR. Stent-graft manufacturers continue to advocate similar surveillance regimens to the pioneers, mainly due to a lack of a robust evidence base to endorse a more efficient alternative.

Significantly more is now known about the overall rates of initial failure of stent-grafts following EVAR, but the mode(s) and timing of these and subsequent failures remain poorly described. This is particularly true after the initial few years following EVAR repair, as prospective cohorts of patients suffer from censoring due to the end of the study follow-up. These issues are exacerbated by poor compliance with surveillance.

Risk of secondary intervention is thought to vary significantly between individuals and within individuals over time. Despite this, generic surveillance regimens are commonly applied to all patients and at all time points following EVAR. Accurately predicting risk for individual patients at different time points would allow much more efficient bespoke surveillance regimens to be created.

While various forms of imaging techniques have been investigated regarding their efficacy to detect individual findings in EVAR surveillance, little is known about which of these findings within these techniques are associated with subsequent secondary interventions to correct or prevent a stent-graft failure.

This study examines the above lacunae, in the published evidence, using a prospective database from the Liverpool Vascular and Endovascular Service (LiVES).

2.1 Background

The randomised controlled trials (RCT) that demonstrated the equivalent efficacy of EVAR to open surgical repair (OSR) reported secondary interventions in the form of the survival metric "freedom from secondary intervention", which is useful when describing the risk to an individual patient.[40-42 45] The UK EVAR trial 1 also reported the overall incidence of secondary interventions throughout follow up, which is useful in health economic calculations that simplify down to mean rates and costs.[36] Neither of these two metrics, however, provide adequate granularity of information to aid the design of an efficient and safe EVAR surveillance programme. The RCTs and subsequent cohort studies also suffer from attrition in patient numbers as follow-up extends, given the nature of prospective studies. Given the knowledge that no one imaging modality is superior in the diagnosis of all complications a more detailed understanding of which complications are likely to occur and at what time following EVAR is required to make an evidence-based decision regarding the optimum imaging modality for and timing of surveillance. An equally important feature of secondary interventions, that requires greater understanding, is which are triggered by surveillance and which are the result of patients self-presenting with symptoms.

Compliance with EVAR surveillance is poor,[70 71] the factors which influence this are poorly understood but are likely a combination of surveillance system factors and patient specific factors. Differences in surveillance imaging regimens in the UK have been well described,[87 88] but no descriptions of the actual administration system used to deliver those imaging regimens exist in the literature. Variation in rates of compliance between centres may be associated with the administartion,[88] centres with high compliance can be presumed to have good surveillance administration systems which allows patient factors to be investigated to identify those independently associated with non-compliance. Such factors would be good targets for patient-based intervention research to see to improve surveillance compliance is achievable.

Colour Duplex Ultrasound Scan (CDUS) and Abdominal Radiography (AXR) are overarching technologies that are the commonest forms of EVAR surveillance imaging in the UK.[88] Large numbers of different observations and measurements can be obtained using CDUS and AXR within EVAR surveillance, despite this diagnostic accuracy studies almost ubiquitously simply refer to the technology and ascribe diagnostic values to them without sufficient description of the specific observations that are used to derived such diagnoses. Little to no description exists in the literature of which

observations on CDUS or AXR are associated with actually triggering a secondary intervention. Understanding which observations are associated with subsequent secondary interventions is key to the accuracy and reproducibility of these surveillance imaging modalities. If multiple observations are being taken during CDUS and AXR that aren't associated with the risk of requiring a secondary intervention, then these observations could potentially be removed from surveillance imaging protocols and improve efficiency of imaging acquisition.

Universal surveillance regimens do not account for the differing risk between patients and within patients' over time following EVAR. Current systems to stratify patients based on their individual risk are all based on a single time point and create binary (high or low) risk profiles, these systems intrinsically offer limited surveillance regimen efficiencies and produce predictions with broad confidence intervals.[89 92] A system that is repeatable at multiple time points following EVAR and that produces an analogue risk prediction would offer the greatest regimen efficiencies, as well as narrower confidence intervals in predication because it can be repeated on multiple occasions during each patients follow-up. Such a system should ideally be based upon findings routinely taken during surveillance using the commonest imaging modality.

2.2 Aims

The aims of this study were to use the prospectively maintained clinical database of patients who have undergone EVAR in LiVES to investigate several lacunae in the evidence regarding EVAR surveillance.

These were:

- Define the nature and timing of secondary interventions
    - Particularly beyond the 5 years following repair (that the majority of published data is limited to).
- Investigate patient compliance with surveillance
    - Establish if patient compliance varies over time in follow-up
    - Establish which patient factors are independently associated with compliance.
- Investigate which findings on AXR and CDUS are associated with a secondary intervention.

- Establish if findings on AXR and CDUS can accurately predict the need, or lack there of, for a secondary intervention over time.

2.3 Methods

2.3.1 Study Design

This was a single centre, cross sectional, data analysis of anonymised data from a prospectively maintained EVAR surveillance database. All patients underwent infra-renal EVAR under LiVES, a city-wide vascular service in the UK. Routine EVAR surveillance is predominately undertaken using CDUS and AXR in LiVES.[78]

2.3.2 LiVES Surveillance Protocol and EVAR Database

LiVES was formed by the combination of the Vascular services from The Royal Liverpool University Hospital, Aintree University Hospital and Southport Hospital in 2012. Prior to their combining the Royal Liverpool University Hospital had maintained a prospective database of all patients who had undergone EVAR since 1996. All patients subsequently undergoing EVAR under LiVES were entered into this database and all patients in the database underwent surveillance to the LiVES protocol.

The database was initially primarily maintained to record the details of the devices implanted into patients however was rapidly adapted to record and administer subsequent surveillance.

2.3.2.1 LiVES Surveillance Protocol

On 1st August 2005 LiVES post-EVAR surveillance was changed from the EUROSTAR and UK-EVAR trials protocols,[93] both requiring annual CTA, to a modified protocol, Table 2 (page 35). This modified protocol involving annual CDUS, to a Standard Operating Procedure (Appendix 1, page 188) and AXR to the Liverpool-Perth protocol,[74] with CTA performed only when potential complications were identified or CDUS was not sufficiently diagnostic. CDUS in place of CTA was well established by the start of the data sample used in this study, in 2008. The change away from CTA surveillance had been closely monitored.[78]

At administration level, the database was reviewed monthly to obtain a list of all individuals who were due surveillance the following month. These individuals were then booked for these investigations. As part of that booking process those who had

died would be identified, by central administrative NHS databases, and the cause of death would be investigated with primary care and recorded in the database.

This search process would also flag all those individuals who are overdue surveillance scans and the cause for this explored, often by an administrator speaking to the patient over the phone but ultimately patients would be recalled to outpatient clinic if no contact could be made.

Patients were actively discharged from the surveillance programme if they were no longer physiologically suitable for any secondary intervention. Dates of transfer to other providers were also recorded if the patient moved out of the area.

Table 2: LiVES EVAR Surveillance Imaging Protocol

Timing	Imaging
Prior to discharge	AXR to Liverpool-Perth Protocol
1 Month after EVAR	CDUS Arterial Phase CTA
12 Months after EVAR and Annually thereafter	AXR to Liverpool-Perth Protocol CDUS Arterial phase CTA -if non-diagnostic or problems identified

2.3.2.2 LiVES EVAR Database

LiVES database contains 3 main tables: patient level data, secondary interventions and surveillance visits. Patients are entered into the database on or shortly after the date they undergo an EVAR. These data pertinent to this study from the patient level table is outlined in Table 3 (page 36), but also includes, for example, serial numbers of the devices used and physicians involved in their procedure. These pertinent data from the secondary intervention table is outlined in Table 4 (page 36), but also included details of whom undertook the procedure and a comments field. Data were entered into the secondary intervention table as and when it came to the attention of the surveillance administrator, as such it was the least comprehensive element of the database.

Table 3: Relevant Patient Level Data Held in the LiVES EVAR Database

Data Field
Unique Hospital Identifier
NHS Number (National Identifier)
Date of Birth
Date of Death
Cause of Death (If Known)
Gender
Patient Post Code
Date of Operation
Pre-op AAA Size (mm)
Pre-op Max Iliac Size (mm)
EVAR Device Implanted
EVAR Device Manufacturer
Date of Discharge from Surveillance
Reason Discharged from Surveillance

Table 4: Secondary Intervention Data Held in the LiVES EVAR Database

Data Field
Unique Hospital Identifier
Date of Intervention
Performed as Emergency
Complication Intervention Treating
Intervention
Laterality (Right/Left/Both)
Patient had symptoms
Complication Detected on Screening

2.3.2.3 Corroborating LiVES Database

It was felt judicious to corroborate these data in the LiVES database as it was not initially intended for audit or research use, although the intended purpose of co-ordinating patient care and recording details of implanted devices demands equally high data standards. As such, where possible, completeness and accuracy of the data in the LiVES database was corroborated from other primary data sources. This was performed as part of a local trust service evaluation reviewing outcomes.

2.3.2.3.1 Patient Level Data

The completeness of the patient list was confirmed by reviewing all coding data and electronic theatre records the trust had available for all aortic aneurysm repairs performed. Review of 2348 coding episodes and 946 electronic theatre records was undertaken. No new patients who had undergone infra-renal EVAR were found. As such a robust patient list was confirmed and used to corroborate other data points.

Date of Birth, NHS number, Date of death, Gender, Postcode and Cause of death were cross referenced against the NHS trusts electronic patient indexing records. Most of these variables are automatically updated from national records (via the "NHS spine"). While a series of typographic errors were found in numeric entries very few omissions were corrected. Date of death was updated in a substantial proportion of patients – likely due to the annual nature of checking by surveillance administrative staff and that if a patient was discharged or moved away these data would not be further updated in the database. Finally cause of death was known within the database for far more patients than the whole trust database, this was likely due to the active checking of surveillance administrative staff with primary care following the demise of a patient rather than the passive trust system that almost exclusively only captures causes of death that occur within the trust.

Patient device and manufacturer were accurately recorded when compared to the paper record of a sample of 348 records. The pre-operative sizes as recorded on the paper EVAR planning sheet was updated when not recorded in the database and was within 0-4mm of the size recorded in the database. This was felt likely to be related to inter-observer variability. A few larger discrepancies were detected but these were in cases where the primary indication was iliac artery aneurysm repair but with concomitant small aortic aneurysm.

Date of discharge from surveillance was only partially verifiable by the date of last surveillance scan (as below) and reasons recorded were only verifiable in recent cases that were accompanied by letters in electronic patient notes.

2.3.2.3.2 Secondary Interventions Data

Secondary intervention data were corroborated from 4 data sources: Coding data, electronic patient notes, electronic theatre records and review of all imaging undertaken within the trust. All 4 sources were only available in combination for a 7-year period during 2008 till 2015 (when this work was commenced). Using the patient data, Section 2.3.2.3.1 (page 37), a list of hospital identifiers (which included multiple / merged identifiers for some single patients) was created from the hospitals' patient indexing system. This list was then used to search the theatre, coding and imaging systems. These were used to create a list of potential secondary interventions which were then verified and corroborated by interrogation of the electronic patient records at the suggested dates. All patients' electronic letters for the entire 2008-2015 period were also reviewed.

Theatre data were used to confirm the date of the original operation when it fell in the available data. The largest variation between the dates recorded in the database and theatre record was 2 days, in these cases the earliest date record was taken to be a true and accurate record. All subsequent operations that occurred after the original EVAR were reviewed for their potential to be a secondary intervention. All subsequent coding episodes after the original EVAR were reviewed and any procedures or admission that may have included a procedure that potentially represented a secondary intervention were reviewed. The imaging performed for each patient on or subsequent to the original EVAR was reviewed. The data points as listed below, Section 2.3.2.3.3 (page 39), were available for all imaging performed.

The reports of all interventional radiology procedures were reviewed, and data recorded for those that represented secondary interventions. With regards to procedures that were prompted by lower limb mal-perfusion (claudication, rest pain or tissue loss): if these included intervention above the inguinal ligament they were treated as secondary interventions - as the placement of EVAR had likely influenced this disease, if all intervention(s) were below the inguinal ligament then this was felt to be peripheral vascular disease not contributed to / worsened by the EVAR.

The report of all surveillance scans were reviewed as discussed below, Section 2.3.2.3.3 (page 39), if these reports included discussion or evidence of a previous secondary

intervention then the previous report was reviewed to create a time frame in which this intervention had occurred and the clinical record reviewed.

Finally, the clinical letters of each patient were reviewed for the time frame and any letters suggesting secondary intervention were planned / had occurred led to further investigation that time frame or record the date of secondary interventions if recorded.

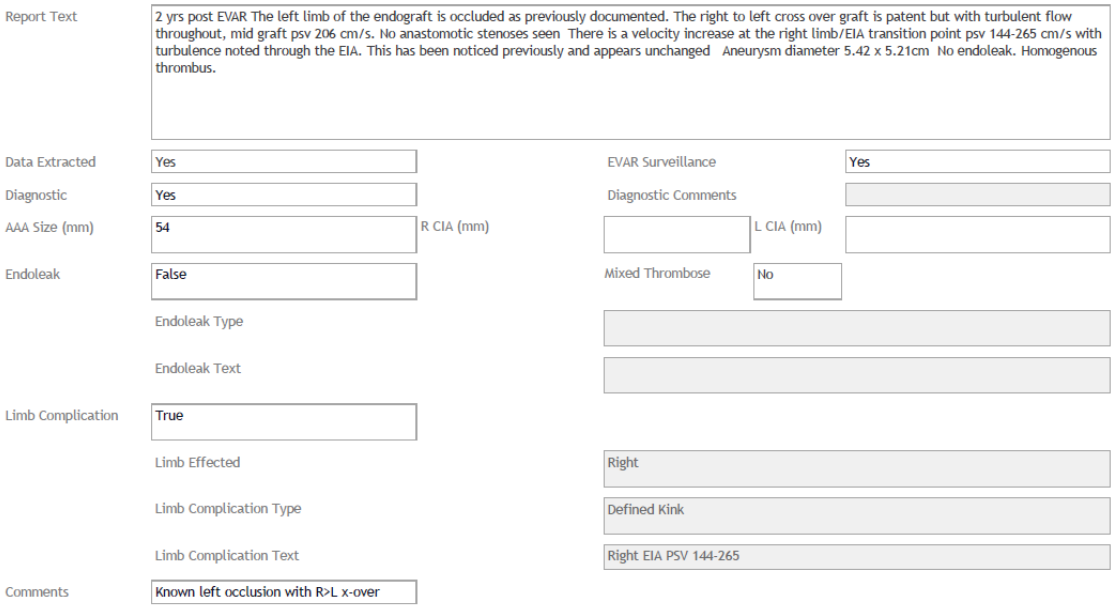
These data sources created a list of potential secondary interventions that were then further investigated by reviewing the clinical notes and source imaging to complete any missing data points, Table 4 (page 36).

A secondary intervention was defined as any surgical or interventional radiology procedure that occurred after the patient had left the theatre for their primary EVAR. These were deemed as emergencies if done outside a planned vascular / interventional radiology list while they remained an inpatient following initial EVAR or if admitted in an unplanned manner following initial discharge. They were deemed symptomatic if the notes recorded symptoms that could be attributable to the complication being treated. If the secondary intervention was precipitated by a surveillance scan this was recorded as detected on surveillance, this was not always a direct trigger: CDUS often suggested a potential complication that then lead to further investigation followed by discussion in a Multidisciplinary Team Meeting (MDT) which then triggered much more intensive surveillance imaging followed by secondary intervention when findings were worsening. This was more often true of flow related complications than aneurysm related complications.

2.3.2.3.3 Surveillance Scans

All radiological reports were retrieved as part of the service evaluation to ensure no secondary interventions were missed. The reports that were for CDUS and AXR as part of EVAR surveillance were broken down to component parts of the report as specified in the standard operating procedure. Figure 8 (page 40) shows a completed example of the, Microsoft Access 356 ProPlus© (Version 1907), form used to break a CDUS written report down to the component sections of the standard operating procedure. When broken down to constituent parts the data processor was therefore completely blinded to the details of outcomes and of that patient as they were not identifiable. Each CDUS reported was broken down to the findings shown in Table 5 (page 41).

Figure 8: Form to Break Down CDUS Report to Constituent Findings



Microsoft Access Form used to break CDUS reports into constituent parts. Anonymised CDUS report displayed at top and user competed constituent parts below.

AXR were acquired according to the Liverpool Perth protocol,[74] which is designed to allow optimum imaging for the diagnosis of those factors outline in the paper. An initial sample of 250 AXR reports were broken down into these constituent parts. The majority of reports were relational, stating that there was no observed difference from a previous set of imaging (or were themselves the baseline imaging). A report stating "No Change" was taken as all these points being negative compared to the last or specified comparator film. After reviewing the comments section of these 250 reports it became apparent that limb kinking was also being detected and reported on AXR so this was added to the pro-forma and all the AXR were broken down to their constituent parts (re-doing the 250 case sample). The findings are displayed in Table 6 (page 42).

The dates of CTAs and the few Magnetic Resonance Angiograms (MRAs) performed were also recorded. These modalities were not reported to a standardised protocol or apparent pattern so were not broken up into their constituent findings.

Table 5: Constituent Part Of CDUS Reports In LiVES EVAR Surveillance, Possible Responses And Data Completeness Levels.

Variable	Responses	Data Completeness (n=3208)
Diagnostic	TRUE or FALSE	100%
Diagnostic Comments	Free text, typically recording why a CDUS was not diagnostic	86.2% (of non-diagnostic scans)
Max AAA Diameter	Size in mm	99.96%
Right CIA Diameter	Size in mm	0.09%
Left CIA Diameter	Size in mm	0.06%
Thrombus in Aneurysm Mixed	TRUE or FALSE	100% (assumed FALSE if not mentioned)
Endoleak Present	TRUE or FALSE	100% (assumed FALSE if not mentioned)
Endoleak Type(s)	Type Ia, Type Ib, Type II, Type III, Other/Unkown	98.9% (of those with endoleak)
Endoelak Text	Free text, typically recording inflow and outflow points if recorded	77.4% (of those with endoleak)
Limb Complication	TRUE or FALSE	100% (assumed FALSE if not mentioned)
Limb Effected	LEFT, RIGHT or BOTH	97.8% (of those with limb complication)
Limb Complication Type	Reduced Flow, Deffined Stenosis, Occlusion	98.8% (of those with limb complication)
Limb Text	Free text, Typically location of stenosis and pre-post PSV or max PSV	94.5% (of those with limb complication)
Comments	General comments on other observations.	10.9%

Table 6: Constituent Parts of AXR Reports in LiVES EVAR Surveillance and Possible Responses

Variable	Reason Recorded	Response
Baseline Image		TRUE/FALSE
Date compared to		Date (coverted to time interval on anonymisation)
Migration	Liverpool Perth Protocol	TRUE/FALSE
Left Limb Kink	Regularly reported - result of sample	TRUE/FALSE
Right Limb Kink	Regularly reported - result of sample	TRUE/FALSE
Structural Failure	Liverpool Perth Protocol (Barb / Strut failure or component seperation)	TRUE/FALSE
Effacement	Liverpool Perth Protocol	TRUE/FALSE
Comment		Free Text
Non-EVAR Finding	Free text of non-EVAR findings	Free Text

2.3.3 Ethical and Research Approval

The Research Department of the Royal Liverpool and Broadgreen University Hospitals NHS Trust granted full sponsorship (reference 5518), the study protocol was peer-reviewed as part of the sponsorship application process.

The study was conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of Good Clinical Practice and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework. The only ethical issue raised by the study was the use of patient's data without consent. This was addressed by the total anonymisation of the data during the research elements so preventing any identification. It is also further mitigated by the fact the researchers worked within the same institution as the patients so meaning there was no external transfers of data. Finally, the patient representative consulted had assumed that there would be, at least conditional, access to these data for research.

The study protocol was reviewed by and a favourable ethical opinion was obtained from the NHS Health Research Authority, National Research Ethics Service, North of Scotland Research Ethics Service, reference 17/NS/0088. Annual progress and final report at conclusion of the study were submitted to the sponsor and ethics committee.

2.3.4 Analysis

Data was processed in Rstudio (version 1.2.5),[94] using R (version 3.6.1),[95] with packages: tidyverse,[96] survival,[97] scales,[98] survminer,[99] Cairo,[100] epitools,[101] caret,[102] MASS,[103] corrplot,[104] mice,[105] ResourceSelection,[106] and DecTools.[107] The full R Code for data processing and analysis is available in Appendix 2 (page 190). The saved results of the Multiple Imputation and other computational data processing are also included to allow exact replication of the results presented. A subgroup of patients who underwent their EVAR after the start of the observational period was created to allow comparison of LiVES outcomes to the published literature.

2.3.4.1 Demographics

Descriptive statistics were used to demonstrate the baseline demographics of the patients included in the study. Year of original EVAR procedure and numbers performed in relation to observational period were plotted using a histogram. Kaplan-Meier survival plot for all patients, and intervention free survival for patients undergoing EVAR within the observational period were created, for comparison to the contemporary literature. Patient distance to the surveillance centre was calculated using the patients' current postcode, or that at the time of death or discharge from EVAR surveillance. This distance is 'as the crow flies' and was calculated using Code-Point® Open,[*] under the Open Government Licence.

[*] Contains OS data © Crown copyright and database right 2018, Contains Royal Mail data © Royal Mail copyright and Database right 2018, Contains National Statistics data © Crown copyright and database right 2018.

2.3.4.2 Nature and Incidence of Secondary Intervention

Each secondary intervention, that occurred during the observational period, was analysed for its trigger, if the patient was symptomatic and to stipulate if it occurred as an emergency. Simple descriptive statistics were used to describe the types and characteristics of the secondary interventions along with the triggers. Secondary interventions were grouped into two broad categories – those intended to preserve flow

through the EVAR stent-graft and those intended to maintain the efficacy of the EVAR stent-graft as a treatment to prevent rupture of AAA.

Finally, the incidence of secondary interventions was calculated using the observational data available in this study. For this analysis patients at risk were established as those who had not been actively discharged from surveillance of the LiVES centre and remained alive for the time points after initial EVAR being assessed. The number of secondary interventions for the previous 12 months were established for each time point from 1.00 year after EVAR and divided by the sum of the number of patient years (or part years) at risk and presented in a graph as an incidence of secondary intervention per 1000 patient years. The analysis was discontinued at 15 years after EVAR, the current limit of the published data.[45] This analysis was then repeated for secondary intervention of each different class to ascertain if the causality of the interventions changed over time. Best fit lines were created using a local regression model, weighted for the number of patient years at risk and calculated using a 0.75 span.[108] Square root of time was used in the model to create the best fit line, this was to account for the known early preponderance of secondary interventions following EVAR.

2.3.4.3 Compliance

The rate of compliance was calculated at each 100th of a year after EVAR. As for the secondary intervention analysis, a list of all patients that were eligible was created for each time point. They were deemed to be “at risk” if they had been alive, not discharged from surveillance and the whole time frame had fallen in the period of observation (ie any surveillance scan would have been captured) for the previous 18 months. Each patient at risk was then tested to ascertain if they had indeed had a surveillance scan and a percentage compliance calculated for that time point. This was repeated for all time points up to 15 years after EVAR.

Patient factors that may be predictive of future compliance were investigated by a similar method. Time points were created for each 10th of a year after EVAR up to 15 years. Each patient alive, after EVAR and not discharged from surveillance, who fell into the observational period who also met those criteria for the following 18 months was deemed at risk. Whether they had any surveillance scan in that 18 month period was used to define compliance (or non-compliance). Patient factors available were then entered into a binominal general linear model to calculate individual variable odds

ratios. These were reviewed individually (unadjusted) to assess them and for comparison to the literature.

Data were then split 80:20 into a training and test group. Individual variables in the training group were recalculated with all variables in the model to get an adjusted odds ratio (to remove confounding between variables). Finally, a stepwise regression was undertaken to remove those variables that had minimal effect on the model to remove the variables that had statistically little effect thereby focusing the model on the most important variables. This effectively removed variables with no effect or close co-linearity with other variables.

This simpler and the original full model were then used in a test group data sample to compare predictive capability and to ensure the removal of these factors had not significantly impacted predictive ability.

2.3.4.4 Surveillance Scan Findings Correlation to Secondary Intervention

To investigate which imaging findings were pertinent to triggering secondary interventions each individual finding was investigated using a univariate survival analysis. The time frame, however, over which this causative effect should be measured was not defined in the literature. As such this was initially defined as described in section 2.3.4.4.1 (page 46).

Individual surveillance scan findings were felt to be more likely to trigger either flow related, or aneurysm related secondary interventions. To prevent surveillance scan findings that trigger rarer (but clinically important) secondary interventions being unreasonably excluded, because of their rarity, aneurysm and flow related secondary interventions were examined separately. Only findings, on surveillance scan, with a perceived causal effect on instigating a secondary intervention were investigated i.e. if a type II endoleak was present was not investigated to look at to see if it instigated flow related secondary interventions, as no causal effect could be hypothesised.

AXR has never been considered an adequate independent surveillance imaging modality and is always used as an adjunct to other modalities, as such AXR variables were considered in relation to the other imaging modality that they were pair with – in LiVES this was CDUS. As such all CDUS scans were paired with the most contemporary AXR, that occurred that day or previously. This allowed assessment of the CDUS variables in conjunction with the AXR findings available at that time.

2.3.4.4.1 Timeframe of Assessment

It is assumed that any finding on an individual surveillance scan is much less likely to be the causal trigger for a secondary intervention as time passes. It was not known how long this effect is present for. While a true finding of a graft related endoleak would logically lead to a rapid sequence of events to trigger a secondary intervention, a true finding of a limb stenosis may lead to an interval scan to assess for progression of haemodynamic effects, multi-disciplinary team discussion, routine clinic appointment to discuss the risks and benefits of intervention with the patient followed by a planned secondary intervention. As such an initial analysis was undertaken to ascertain the global risk of secondary intervention following a surveillance scan.

This was performed, by first creating a Nelson–Aalen estimator of the cumulative hazard ratio of secondary interventions for the 2 years following surveillance scan. This was then converted into an actual point hazard ratio at individual time points following the scan. This individual time point hazard ratio was created through the conversion of a best fit line, fitted to the Nelson-Aalen estimator. The time of accelerated secondary interventions was observed in the first 6 months following the scan before the baseline risk of secondary intervention was seen.

The early preponderance of surveillance imaging and high percentage of observed secondary interventions immediately following EVAR risked influencing this analysis. To ensure there was no selection bias in the observed relative hazard ratio, the analysis was repeated for surveillance scans that had occurred at least ¾ year or later after initial EVAR, chosen based on data in Figure 11 (page 54). This confirmed the same interval to be appropriate even after the immediate post-op period.

2.3.4.4.2 Findings on Surveillance Scans that Correlated with Secondary Interventions

Data were censored at the time of a secondary intervention that was not in the group of interventions being assessed in that analysis (flow related, or aneurysm related). This was due to the assumption that a patient who underwent a secondary intervention [for another reason] was likely to have had a further surveillance scan following that intervention so findings were potentially being assessed twice. In categorical variables survival analysis was undertaken in the form of Kaplan–Meier survival plot and log rank test for categorical variables, if multiple variables (in categorical variables) were similar they were grouped together if this was a clinically logical grouping. Results of Cox proportional hazard models were reported as hazard ratios, 95% confidence interval

of that hazard ratio and p values. Continuous variables survival analysis was more complex due to less complete data. In variables with complete data, Cox proportional hazard models were fitted using the continuous variables. Results of Cox proportional hazard models were reported as hazard ratios (per described increment), 95% confidence interval of hazard ratio and p values

2.1.1.1.1.1 Missingness and Multiple Imputations

Missing values can be absent for many reasons but the cause of its missingness can introduce bias into statistical analyses. Missing data is therefore usually classified into one of three categories:

- Missing Completely at Random
- Missing at Random (MAR)
- Not Missing at Random (NMAR)

Missing Completely at Random data will introduce no bias to analyses as it is completely random. MAR data do not depend on the unobserved values of these data but do depend on these observed data so analysis of all these data will compensate for these MAR data due the relationship between these available data and MAR data. NMAR, is essentially non-response bias, meaning these missing data will introduce bias to analysis if not compensated for.

For categorical variables data missingness was grossly assessed by event rates in the missing data compared to the other categories. If the event rate was notably different then an assumption of NMAR was made and multiple imputation methods were used in analyses.

In continuous variables a dummy binary variable (0 for missing or 1 for present) were created for data missingness and any missing variable replaced with a numerical 0 value. The missingness binary variable was divided by the variable being investigated in the formula of a Cox proportional hazard model with the time and event data. If for any of the created models the missingness variable became statistically significant this was interpreted as data potentially being NMAR. In such cases multiple imputation was undertaken as detailed below. If not, data was taken to be MAR. If no data was missing or data was MAR, analysis was undertaken using the original data with cases omitted that had MAR data and any associated events.

Multiple imputation was used in cases of data NMAR. It reduces uncertainty created about missing values by creating several versions of the same data set and calculating several likely imputations or replacements for the missing values. These versions are then subjected to the required statistical analysis. The output of this analysis is then "pooled" and the most likely outcome reported. This improves validity and increases precision.

Within this study, multiple imputation was undertaken using the "mice" package (Version 3.6.0) in R.[105] This uses "chained equations" to form its multivariate imputations. Chained equations specify the statistical model type, that creates the imputation, separately for each variable with missing data, these models can follow different distributions or methods. MICE loops through an iterative process: In the first iteration, the model for the variable with the least missing values is estimated using only complete data. Next, the variable with the second least missing values is imputed using the complete data and the imputed values from the last iteration. After each variable has been through this process, the cycle is repeated using the data from the last iteration. After the last cycle is completed the values are saved as one imputed data set.

Within this study continuous (numeric) variables were iterated by a predictive mean matching model, logical (True/False) by Bayesian logistic regression model and unordered categorical variables by Bayesian polytomous logistic regression model. All the models were constructed with input from all the variables in the dataset being used, including the outcome variable.
Predictive mean matching forms a small set (5 in this study) of candidate donors, from all complete cases, that have values closest to the other variables for case with the NMAR variable. One donor is randomly drawn from the candidates, and the observed value of the donor is taken to replace the NMAR variable. The assumption is the distribution of the missing cell is the same as the observed data of the candidate donor.

500 imputed datasets were generated given the modest amount of computing power required to generate a single set.

2.1.1.1.1.2 Assessment of Co-Linearity and Confounding Between Variables that Could Allow Rationalisation of Variables

It was envisaged that variables were likely to have confounding or co-linearity between them in relation to secondary interventions. As such a multi variable Cox proportional hazard model was created for both flow related and aneurysm related secondary

interventions to assess for these and rationalise these variables to those, that combined offer the highest predictive ability and therefore likeliest, when measured, to aid clinicians in identifying the need for secondary intervention. This was undertaken using a backwards stepwise procedure using: clinical knowledge, hazard ratios and p values to select the order of candidate variables for exclusion. The multiple imputed data was used to assess each new iteration till backwards exclusion of further variables increased the Akaike information criterion (AIC) by greater than 4. The hazard ratios and p values for each variable in the simplified and full models are reported, however it is highlighted that the model is being used as a surrogate for the clinician decision making processes to assess the impact of less data being collected or being available for decisions.

This simplified model was assessed in comparison to the full model based on two characteristics: calibration and discrimination. Calibration was assessed by visual scatter plot comparison of the simplified and full model numeric predictions using all sufficiently complete data. This relationship was then quantified by a linear model with reporting of the co-efficient and numeric offset for comparison. Discrimination was assessed by ROC curve production and AUC calculation for both models for comparison.

2.3.4.5 Creation of Model to Predict Secondary Intervention

To find if future risk of secondary intervention could be accurately predicted a model was created and internally validated. Given that the risk of secondary intervention had already been established to be variable over time a single model that covered all time points was felt unlikely to achieve the high predicative ability demanded in clinical use. As such a Piecewise Exponential Model (PEM) was used.

2.3.4.5.1 Piecewise Exponential Model

The PEM, as proposed by Freidman et al.,[109] is a methodology for modelling risk under an assumption of proportional hazards but with the inclusion of a parametric form for the underlying hazard function. It is often preferred over the more standard Cox model when absolute levels of risk are of interest as well as relative measures between covariate levels (e.g. hazard ratios). While simpler parametric models are available, these can lack the flexibility of the PEM to accurately model changes in risk, within subjects, over time.

The PEM was constructed, by Dr R Jackson, by first defining a time grid, a partition of the time axis into a number of segments or timeframes. Within each time frame, an exponential parameter is fit under the assumption that the underlying risk of an event remains constant. The definition of the time grid partitions was set according to clinical relevance, for example setting a partition (0- 6 months) will allow for the risk of an event within the first 6 months of the period of interest. Within each segment, the model fit is analogous to log-linear regression. Here the number of events can be assumed to follow a Poisson distribution and the underlying risk is estimated by the number of events observed as a ratio of the total patient time at risk in that segment. Including covariates into the model allows for the baseline risk to be adjusted due to clinical/prognostic factors of interest as with standard regression. The effects due to these covariates are considered to be equal across all segments of the time grid and do not differ between time segments. The parameters for the underlying risk, of an event, then define the average risk for each time-segments and along with adjusting covariates can lead to estimation of predictive event rates in a way that Cox models are unable to achieve. Estimation of model parameters are obtained via standard maximum likelihood approach.

2.3.4.5.2 Piecewise Exponential Model Creation

The time frames for the PEM were primarily set based upon the relevant findings in the incidence of secondary interventions, Section 2.4.2.2 (page 57). The number of patients at risk at given time points was a secondary consideration to ensure enough data fell within each time frame for model creation and validation.

All variables from the previous CDUS analysis, Section 2.3.4.4 (page 45), Table 16 (page 93) and Table 17 (page 94), were available in the model creation. In addition, a number of patient variables were also available (Table 7, page 52). Model creation was undertaken on the principle of using the minimum number of variables needed to acquire the best AIC, trial selection and elimination in a stepwise manner were based on the previous findings in this study and published knowledge. Each step that rendered a decrease in AIC was compared directly with the X^2 distribution. With a decrease of 4 or more being indicative of a co-variate worth retaining in the model.

2.3.4.5.3 Internal Validation

The validation of the PEM examined 2 characteristics, the first was the calibration of the model. Calibration is the measure of agreement between observed outcomes and

predictions. The second characteristic is discrimination, this is the PEMs accuracy in predicting who will develop an event earlier and who will develop an event later (or not at all).

Internal validation was undertaken using a bootstrap technique. The data were randomly split 80:20 for model training and validation, respectively. This process was repeated 5000 times. On each of these occasions; the model was re-fitted (relative weighting of variables adjusted) on the model training data set, a Receiver Operator Characteristics (ROC) with an Area Under The Curve (AUC) to assess discrimination and Hosmer–Lemeshow test to assess calibration were then calculated on the validation data set. The relative weighting of the variables, area under the curve and Hosmer–Lemeshow test p value, respectively, were recorded for each of the 5000 repeats. ROC was used to assess discrimination, this is the PEMs accuracy in predicting who will develop an event earlier and who will develop an event later (or not at all) calibration was assessed using Hosmer–Lemeshow test p value, which should be non significant, a significant value signifies a significant number of patients had an event that the model did not predicted. The co-efficient (estimate and standard error) and p value for each variable in the model was recorded for each round of internal validation. The mean of these recorded values is reported.

Finally example prediction graphs where produced to demonstrate the models potential practical clinical use. Assessment patients were created for this purpose with low, mean and high risk findings to demonstrate how risk predictions would be displayed. The values used for these patients was the first quartile, median and third quantile from the original dataset for each variable used in the model.

2.4 Results

The anonymised data from the LiVES database and imaging variables are available in Appendix 3 (page 235).

2.4.1 Demographics

Table 7 (page 52) demonstrates the patient variables for all infra-renal EVAR patients in the LiVES EVAR database.

LiVES performed less than 25 EVAR cases a year till 2005, then there was an increasing use up to a maximum case load of between 100 – 115 between 2009-2011, this then slowly declined to ~60 cases a year by 2014, Figure 9 (page 53). Numbers of

patients that had their primary operation before or during the study observational period of the study are displayed in differing colours. All cause survival following EVAR follows a broadly linear decline from 100 to ~20% over 18 years, Figure 10 (page 54). Freedom from secondary intervention can only be reliably calculated for those patients who had a procedure after 2008, the start of this studies observational period. Freedom from secondary intervention shows a sharp decline to approximately 90% in the first 6 months then grossly linear decline to approximately 75% over the following 5 years, Figure 11 (page 54).

Table 7: LiVES Surveillance Database - Patient Demographics

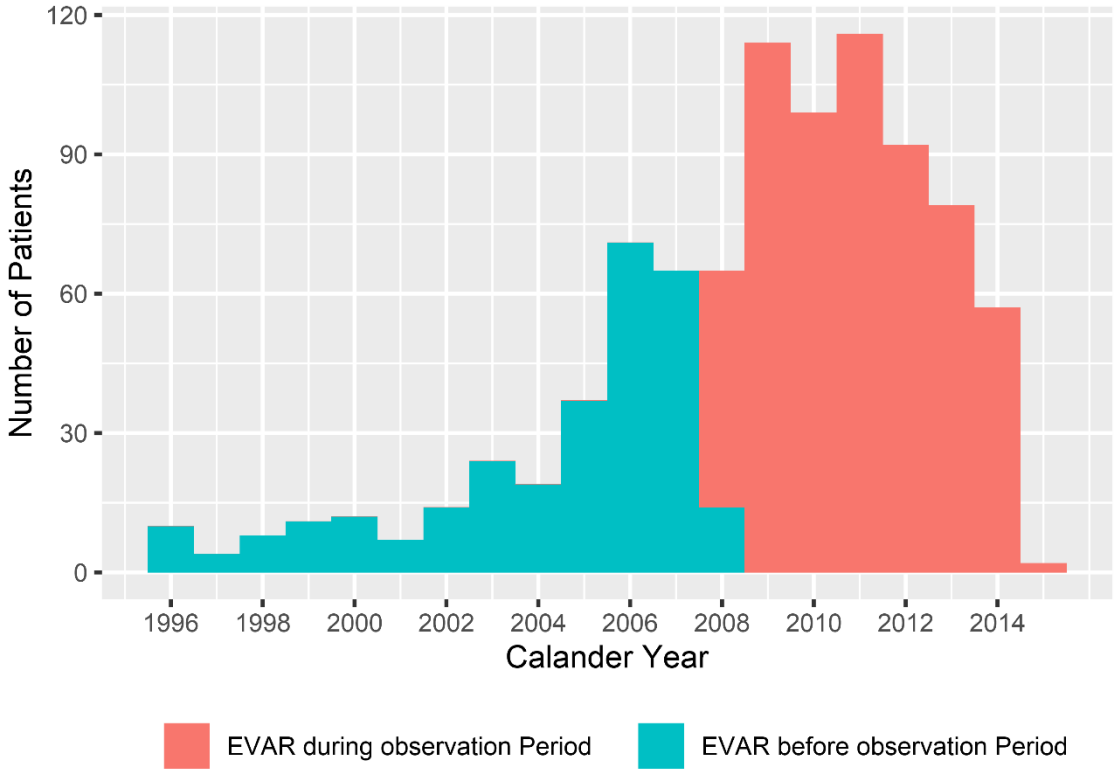
Variable	Median (IQR)	Data Completeness
Calander Year of Operation	2009 (2007-2012)	100%
Age at Operation (years)	76 (71 – 81)	100%
Gender	86.5% Male	100%
Pre operative max AAA size (mm)	62 (57 – 70)	94%
Pre operative max iliac size (mm)	17 (14 – 20)	32%
Distance to surveillance centre (km)	11.5 (6.38 – 22.63)	95%

Of 906 cases, the manufacturer of the device implanted was Cook Medical (Bloomington, Indiana, U.S.A) in 415 cases, Medtronic (Dublin, Ireland) in 292 cases, W. L. Gore and Associates (Newark, Delaware, U.S.A) in 158 cases and others in 41 cases. The 6 most common individual device types use are listed in Table 8 (page 53).

Table 8: LiVES EVARs – 6 Commonest EVAR devices

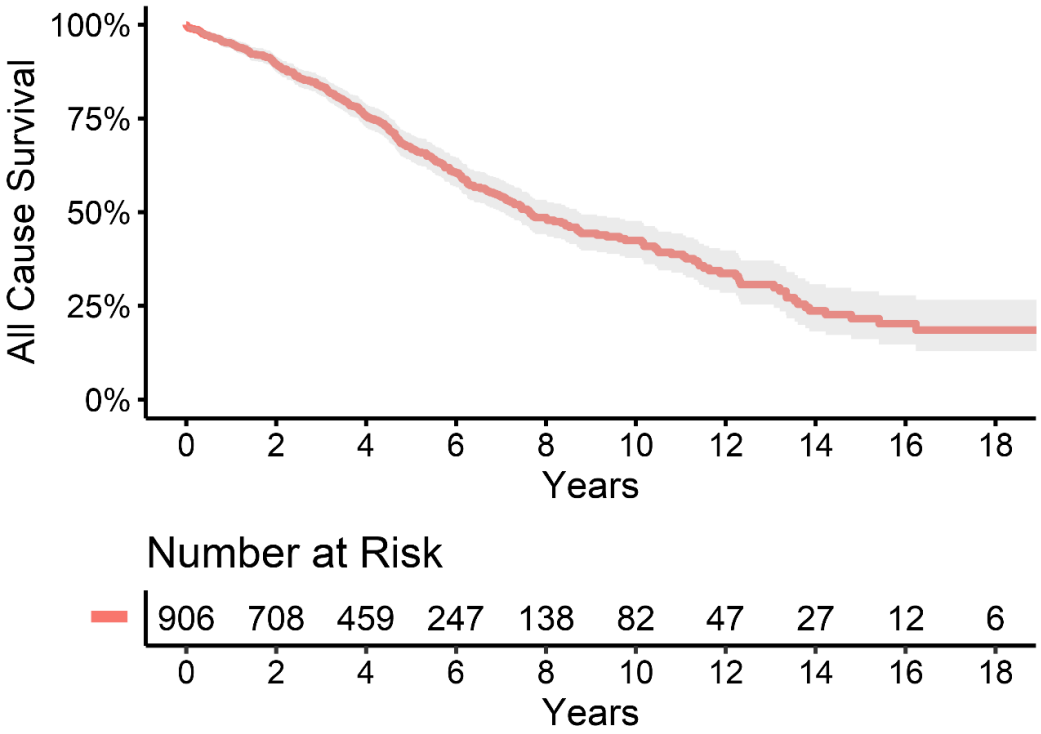
EVAR Device	Manufacturer	Number (% of Total)
Endurant	Medtronic	206 (23%)
Zenith Flex	Cook Medical	192 (21%)
Zenith	Cook Medical	144 (16%)
Excluder C3	Gore	97 (11%)
Endurant II	Medtronic	59 (7%)
Excluder	Gore	54 (6%)
Others	-	154 (17%)

Figure 9:Histogram of EVARs performed in LiVES for each calendar Year



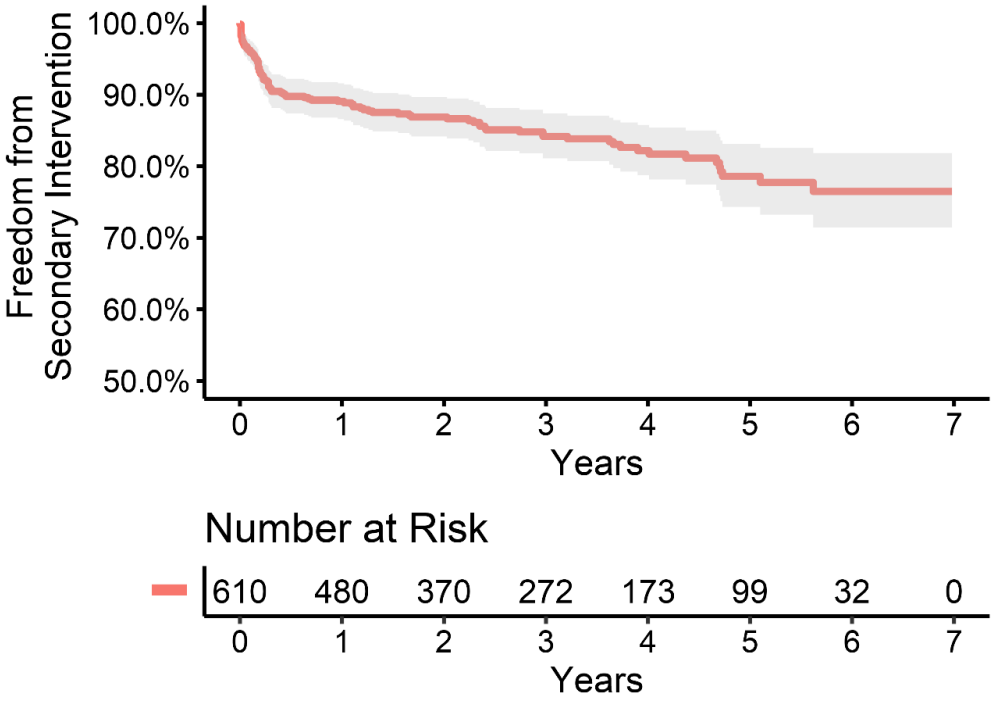
Histogram of number of EVARs performed in LiVES per calendar year between 1996 and 2015. Cases are differentiated by if they were performed before or during the period of the observational study, the majority being during the study.

Figure 10: All cause survival following EVAR in LiVES



Kaplan-Meier plot demonstrating a grossly linear decline in all cause survival, to ~25% by 14 years, following EVAR in LiVES

Figure 11: Freedom from Secondary Intervention Following EVAR in LiVES



Kaplan-Meier plot demonstrating freedom from [any] secondary intervention following EVAR in LiVES deteriotes to 90% with 6 months then in a linear fashion to 80% by 5 years.

2.4.2 Secondary Interventions

2.4.2.1 Nature of Secondary Interventions

A total of 178 secondary interventions occurred during the 7 year period observed in this study. These secondary interventions occurred in 119 unique individuals. They occurred between 0.00 and 16.46 years after initial EVAR procedure. Of these 24 (13%) cases were treated as an emergency, 9 of which occurred prior to discharge from the initial EVAR. Of 178 secondary intervention in this observational period only 15 (8%) resulted in a new emergency admission.

The patient had symptoms in 44 (25%) of 175 interventions that could be interrogated, 3 cases had no clinical notes/correspondence to review and while the procedure and indication could be ascertained from imaging the presence/absence of symptoms was unlikely to have been recorded in those locations. Of these 44, 15 had symptoms on direct questioning but had failed to self-present or waited till their next surveillance visit to voice their symptoms. The remaining 29 cases either self presented or had incidental findings on non-surveillance imaging that prompted referral and treatment.
Patients were asymptomatic of their complication in 131 (75%) of the interventions. Only 7 of these asymptomatic interventions were not deemed the direct result of surveillance imaging. These 7 were the result of findings on non-surveillance imaging that promoted referral back to the LiVES service.

Secondary interventions fell broadly into 2 main categories: Those intended to maintain the efficacy of the aneurysm treatment and those intended to maintain distal perfusion through the stent-graft to the lower limbs. Further procedures to treat complications of a secondary intervention were labelled under the category of the initial secondary intervention. 86 (48%) were to treat flow related complications and 92 (52%) were to maintain aneurysm treatment efficacy, Table 9 (page 56). Of these secondary interventions 128 (72%) were endovascular and 43 (28%) were open surgical procedures, Table 10 (page 57).

Table 9: Indications for Secondary Interventions follow EVAR in LiVES

Indication	Number of Secondary interventions (% of Total n=178)
Maitaining Aneurysm Treatment Efficacy (n= 92)	
All Endoleaks	68 (38%)
Type Ia	12
Type Ib	15
Type II	23
Type III	10 (1 not present at intervention)
Uncharacterised Endoleak	3
Endotension	5
Rupture	3 (2%)
Impending Failure	12 (7%)
Effacement	*4*
Migration	*8*
Various immediate post procedure complications	9 (5%)
Maintaining Flow (n=86)	
Limb Stenosis (6 not confimred on angiography)	60 (34%)
Limb, CFA or Bypass Oclussion (Including 2 acute limb ischemias)	21 (12%)
Pseudoaneurysm or peripheral bleeding	5 (3%)

Table 10: Cross-Section of Secondary Interventions at all times after EVAR in a single Tertiary UK Vascular Centre

Secondary Intervention	Number of Secondary interventions (% of Total n=178)
Endovascular Interventions	128 (72%)
Limb Stenting	45
Limb Extension	22
Endoleak Embolisation	21
Angiogram - No Intervention Performed	12
Limb Angioplasty	8
Relinning (+/- FEVAR cuff)	8
Proximal Endovascular Cuff	7
Palmaz Stent	2
Isolated Viseral Artery Interevention	2
Thrombectomy and Limb Stenting	1
Open Vascular Surgery	43 (24%)
Arterial Bypass	17
Open AAA Conversion / Repair	15
Surgical Pseudoaneurysm Repair	5
Femoral artery Endarterectomy	4
Fasciotomy	1
Major Limb Amputation	1
Abdominal Surgery	7 (4%)
Colectomy	**4**
Other Laparotomy/Laparostomy	**3**

2.4.2.2 Incidence of Secondary Interventions

Calculation of the number of patient years at risk was undertaken, Table 11, (page 58), shows the sum of all the complete and partial patient years that were at risk in the previous 12 months. This shows 567 patient years at risk in the first 12 months decreasing relatively linearly to 16.5 patient years in the 12 months up to 15 years post EVAR. Averaged throughout follow-up this represents 61.3 interventions per 1000 patient years.

Table 11: Number of patient years at risk at differing time points in observational study following EVAR

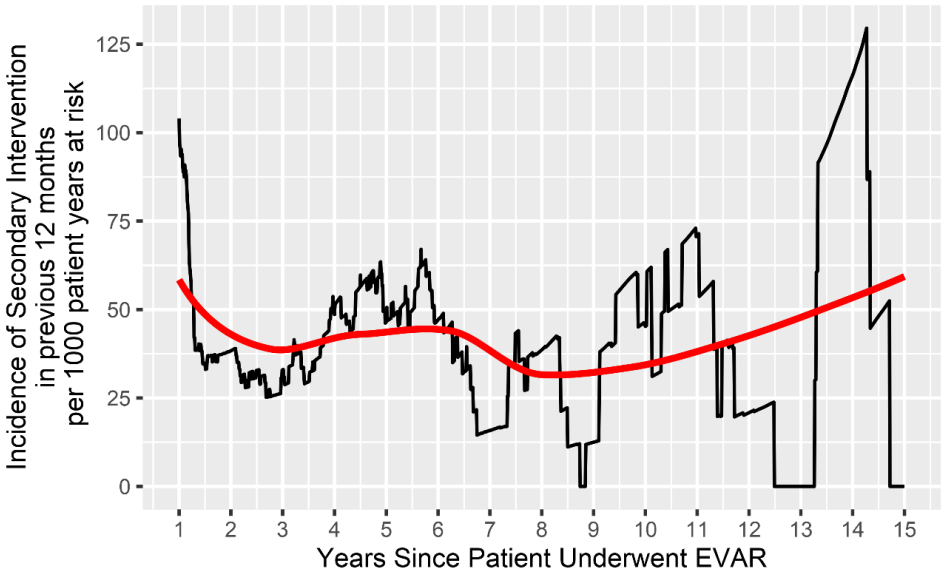
Years following EVAR	Number of patient years at risk in previous 12 months
1	567.0
2	521.2
3	454.9
4	349.9
5	257.9
6	190.9
7	126.8
8	103.6
9	79.9
10	66.35
11	56.4
12	47.95
13	36.4
14	25.8
15	16.5

There is modest variance in the trend in secondary interventions between approximately 60 and 30 secondary interventions, in the previous 12 months, per 1000 patient years at risk, Figure 12 (page 59). This variance takes the form of an initial downward trend between years 1 to 2 ½ years from 60 to approximately 35 events, where it remains relatively static until a more gradual upward trend in years 9 to 15 takes the rate back up to approximately 60 events.

The incidence of secondary interventions following EVAR classed as aneurysm related and flow related are demonstrated in Figure 13 (page 59) and Figure 14 (page 60) respectively. Aneurysm related secondary interventions are initially rare, ~12 events per 12 months increasing to 25 events by year 3 and then relatively static thereafter. Flow

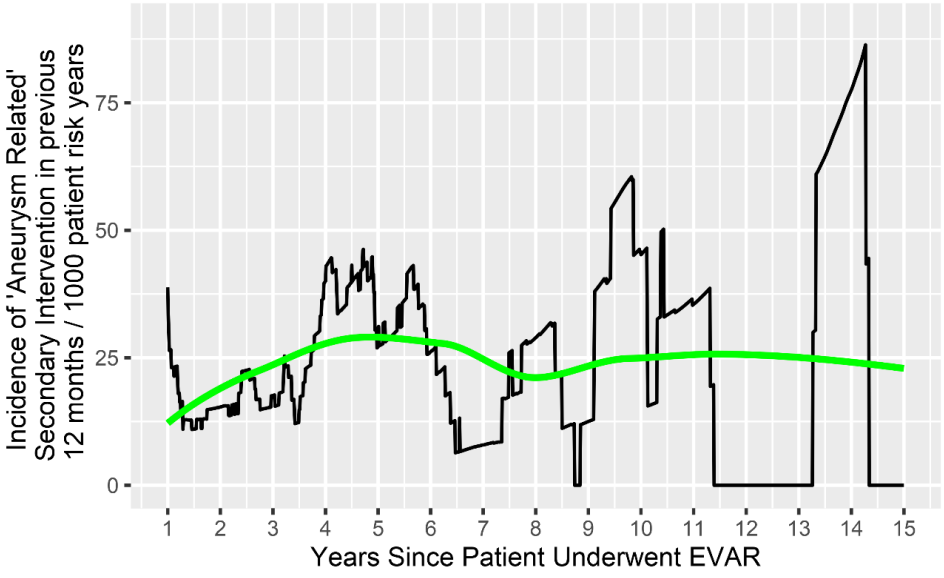
related secondary interventions are very frequent initially with an event rate of 50 in the first year which quickly reduces to approximately 12 by year 3. This remains somewhat static till year 11 when it then gradually increases again, reaching 30 events by year 15.

Figure 12: Incidence of Secondary interventions in the previous 12 months at differing time points following EVAR, with trend line



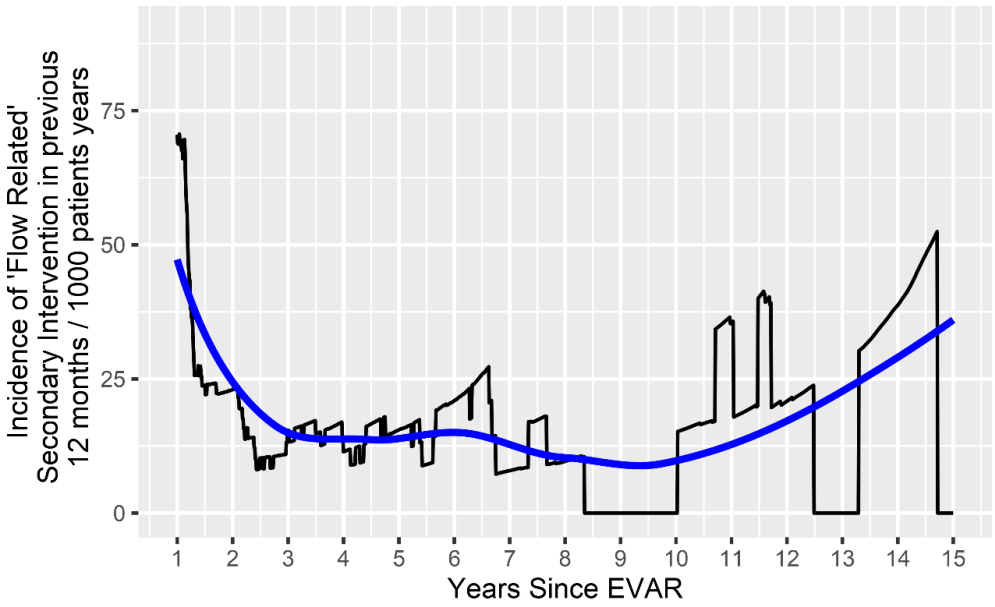
Black line: true incidence of any secondary interventions in previous 12 months per 1000 patient years at risk. **Red Line**: line of best fit weighted by number of patient years at risk.

Figure 13: Incidence of Aneurysm Related Secondary Interventions in the Previous 12 Months Following EVAR, with trend line



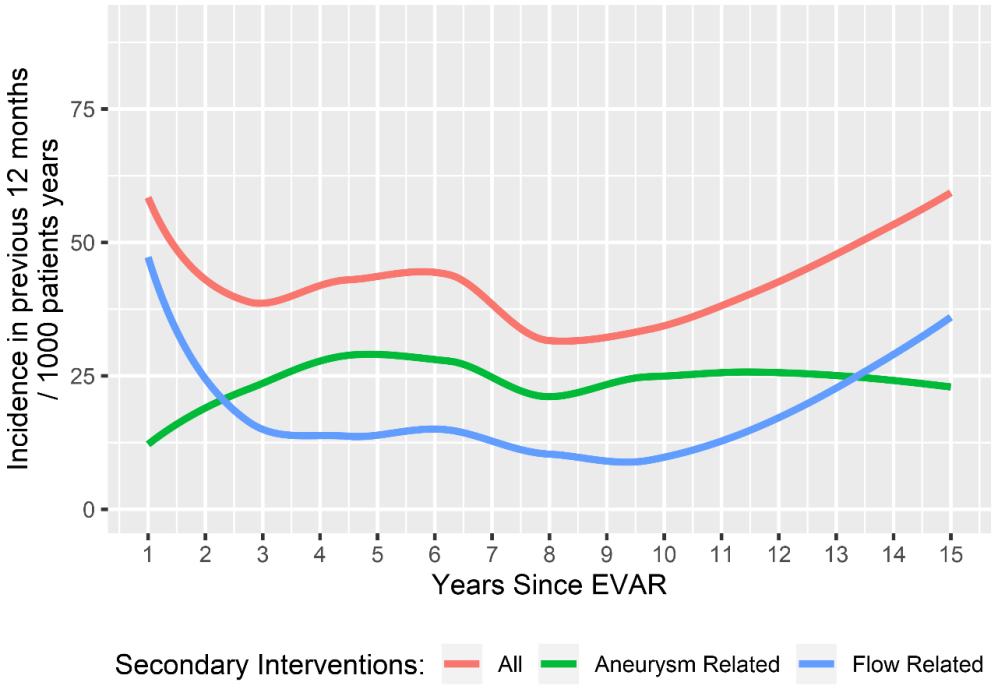
Black line: true incidence of aneurysm related secondary interventions in previous 12 months per 1000 patient years at risk. **Green Line**: line of best fit weighted by number of patient years at risk.

Figure 14: Incidence of Flow Related Secondary Interventions in the Previous 12 Months Following EVAR, with trend line



Black line: true incidence of flow related secondary interventions in previous 12 months per 1000 patient years at risk. **Blue Line**: line of best fit weighted by number of patient years at risk.

Figure 15: Trend Lines of Frequency, by Type, of Secondary Intervention Following EVAR



Lines of best fit, weighted by number of patient years at risk, of incidence of secondary interventions of defined type in the previous 12 months per 1000 patient years at risk. Demonstrating the varying indications over time after EVAR.

The trend lines of frequency for: flow related, aneurysm related and all secondary interventions are presented in Figure 15 (page 60). This allows the direct comparison of the differing event rates over time. They demonstrate that the early predominance of secondary interventions is caused by flow related secondary interventions. This is somewhat offset by a low initial rate of aneurysm related secondary interventions, which by year 3 remain static in available analysis. The increasing rate of secondary interventions from year 10 onwards happens almost exclusively as the result of flow related secondary interventions.

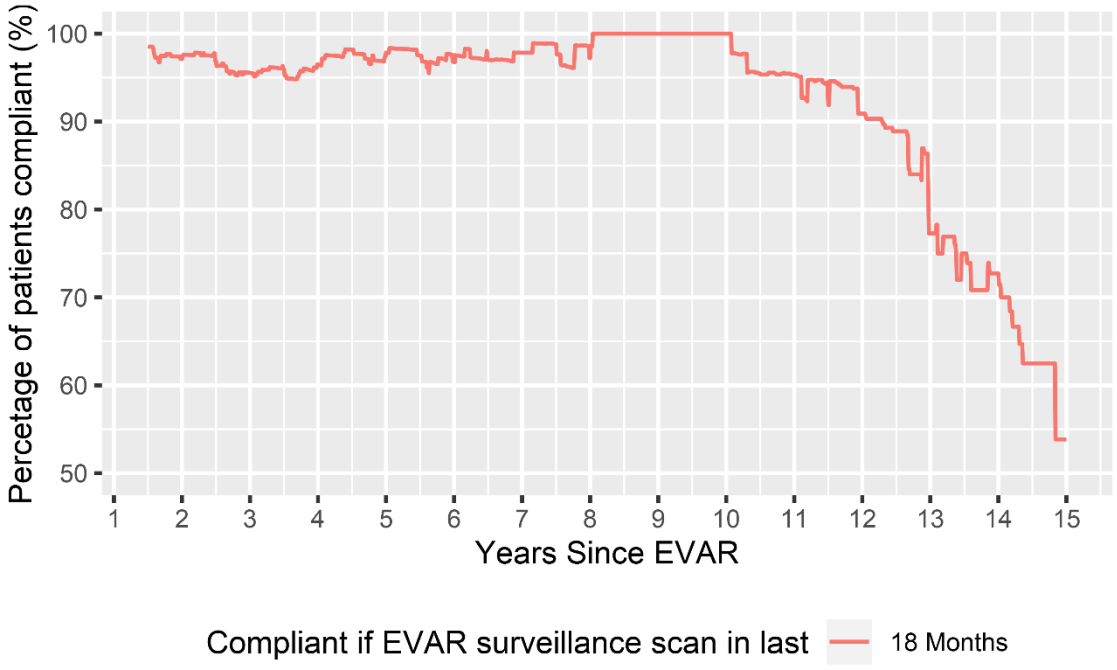
2.4.3 Compliance

A total of 13,817 imaging events occurred during the observational period and were reviewed. They occurred in 849 individuals who had undergone EVAR in LiVES. 7,387 of the 13,817 imaging events were deemed to be related to EVAR surveillance. Of these 3,062 AXR's and 114 CEUS studies were not felt sufficient to be classified as surveillance in their own right. A total of 3256 CDUS, 947 CTA and 8 Magnetic Resonance Imaging Angiograms (MRA) were all deemed to constitute surveillance visits for this analysis. Many of these imaging modalities will have occurred on the same day. The MRA scans were all conducted with concomitant AXRs.

2.4.3.1 Compliance Following EVAR

The rate of compliance, defined as a specific surveillance scan within 18 months, over time following EVAR is present in Figure 16 (page 62). It demonstrates excellent compliance, in excess of 95% until year 10, then a near linear reduction in compliance from years 10 to 15 reaching ~55% compliance by year 15. Table 12 (page 63) presents the number of patients at risk, in whole year intervals, for this compliance analysis.

Figure 16: Compliance with EVAR surveillance: Percentage of patients to have undergone a Surveillance scan in the previous 18 months



Graph of percentage of patients at risk who were compliant with surveillance imaging in the previous 18 months for different times after EVAR up to 15 years. Shows >95% compliance till 10 years after EVAR then gradual decline to <55% by 15 years.

Table 12: Number of patient years at risk at differing time points for compliance analysis

Years following EVAR	At risk for 18 Month definition of compliance
2	381
3	337
4	255
5	186
6	123
7	92
8	72
9	53
10	45
11	43
12	33
13	22
14	22
15	13

2.4.3.2 Patient Characteristics Associated with Future Compliance

These data were used as described in the methods section for fitting a binomial regression model.

Using these data, odds ratios were then calculated for future compliance in both unadjusted and adjusted (for other variables) forms. Adjusted Odds ratios were calculated using a model utilising all the described variables, thereby accounting for confounding between variables. The exclusion of the variable “Age at Operation” is the result of absolute co-linearity with “Age at Surveillance Scan” and “Time after EVAR”.

Table 15 (page 65) demonstrates the Odds ratios of the most important variables that were left after stepwise regression modelling. This simplified and the original full model were then used in the test data sample to compare their predictive capability and

to ensure the removal of these factors has not impacted predictive ability. The full model and the simpler stepwise model both accurately predicted compliance in 81.7% of cases in the test sample.

Table 13: Data points and Distribution Used in Analysis Determining Patient Factors Associated with Surveilliance Compliance

Variable	Median (IQR)	Data Completeness
Calander Year of Operation	2009 (2006-2011)	100%
Age at Operation (years)	75 (70 – 80)	100%
Age at Surveillance Scan	78.9 (74.2 – 83.8)	100%
Time after EVAR	2.8 (1.3 – 5.1)	100%
Gender	87.6% Male	100%
Pre operative max AAA diameter (mm)	62 (57 – 70)	95%
Distance to surveillance centre (km)	11.78 (6.20 – 23.30)	96%
Previous Secondary Intervention	12.8% TRUE	100%

Table 14: Unadjusted and Adjusted odds ratios, of patient variables, for future compliance with EVAR surveilence.

Variable	Unadjusted Odds Ratio for EVAR Surveillance compliance (95% CI)	Adjusted Odds Ratio for EVAR surveillance compliance (95% CI)
Calander Year of Operation (per year)	0.97 (0.96-0.98)	0.67 (0.66-0.685)
Age at Operation (per year)	0.975 (0.97-0.98)	-
Age at Surveillance Scan	0.95 (0.95-0.96)	0.96 (0.96 – 0.97)
Time after EVAR (per year)	0.91 (0.90-0.92)	0.62 (0.60-0.63)
Gender (MALE)	1.05 (0.95 -1.17)	1.02 (0.91 – 1.14)
Pre operative max AAA size (/mm)	1.00(0.995 – 1.00)	1.00 (1.00 -1.00)
Distance to surveillance centre (/10 km)	1.02 (1.01-1.03)	1.00 (1.00 – 1.00)
Previous Secondary Intervention	0.91 (0.82-1.01)	1.13 (1.01 – 1.25)

Table 15: Variables which influence compliance following a stepwise regression of full model.

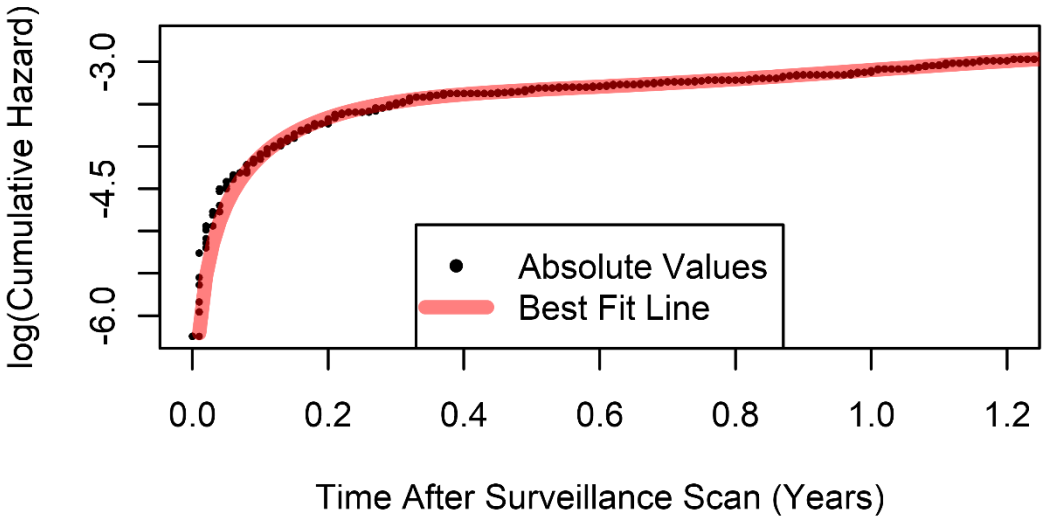
Variable	Final Odds Ratio	Statistical Significance (p)
Calander Year of Operation (/year)	0.67 (0.66-0.685)	>0.001
Age at Surveillance Scan (/year)	0.96(0.96-0.97)	>0.001
Time after EVAR (/year)	0.60 (0.60-0.61)	>0.001
Distance to surveillance centre (/10 km)	1.03 (1.01-1.04)	>0.001
Previous Secondary Intervention	1.13 (1.01-1.26)	0.03

2.4.4 Surveillance Scan Findings Correlation to Secondary Intervention

2.4.4.1 Interval of Effect

3092 CDUS scans in 756 individuals were considered, secondary intervention data were right censored at 2 years- as the maximal time that any effect of CDUS on secondary intervention rates could be conceived. 168 scans were followed by a secondary intervention in this available follow-up to 2 years. The best fit line to the Log conversion of the Nelson-Aalen cumulative hazard estimator, Figure 17 (page 66), demonstrates an inverse exponential function with the majority of the risk accumulated by 0.3 years and linear accumulation of risk definitively established by 0.5 years onwards.

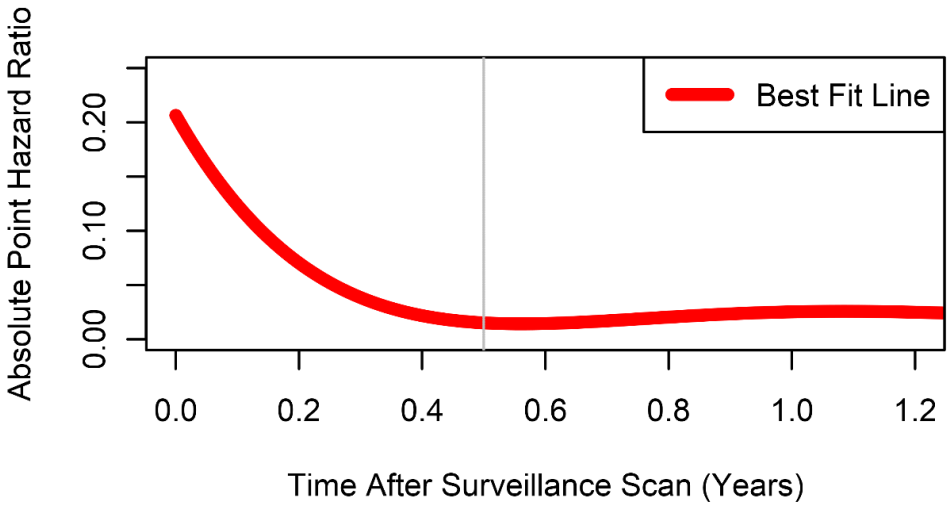
Figure 17: Cumulative Hazard Ratio of Undergoing Secondary Intervention Following Post Operative EVAR Surveillance Scan



Black Points: Log conversion of a cumulative hazard estimator points - of requiring a secondary intervention following an EVAR surveillance scan. **Red Line**: best fit line demonstrating an inverse exponential function of hazard as time passes.

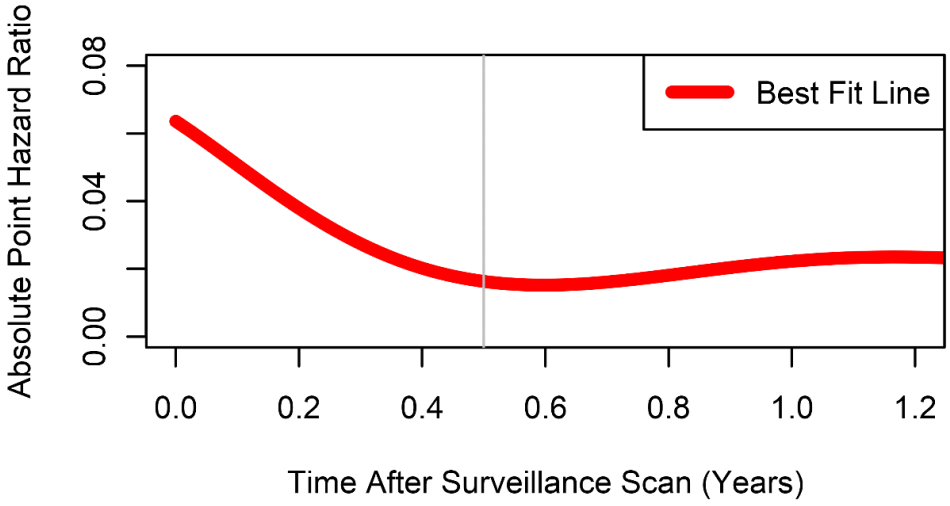
The best fit line was then transformed into absolute point (in time) hazard ratios. This absolute point hazard ratio, Figure 18 (page 67), demonstrate an increased hazard of secondary intervention following surveillance scan followed by a gradual reduction in hazard down to a stable baseline hazard by 0.5 years, which then remains essentially static.

Figure 18: Point Hazard Ratio of Undergoing Secondary Intervention Following Post-Operative EVAR Surveillance Scan



Absolute risk or requiring a secondary intervention at any given time after EVAR surveillance scan, showing very high risk immediately following surveillance scan but settling to a relatively low baseline risk by 0.5 years after scan.

Figure 19: Point Hazard Ratio of Undergoing Secondary Intervention Following Post-Operative EVAR Surveillance Scan That Occurred at Least 0.75 Years Following EVAR.



Absolute risk or requiring a secondary intervention at any given time after an EVAR surveillance scan, when at least 0.75years after initial EVAR. Demonstrates a moderate risk immediately following surveillance scan but settling to a low baseline risk by 0.5 years after scan.

This entire hazard analysis was repeated for surveillance scans that occurred at least 0.75 years following that individuals initial EVAR procedure. This repeat analysis was designed to remove any confounding that may have occurred due to the co-linearity of secondary interventions and surveillance scans immediately following initial EVAR procedure. The repeat analysis was undertaken on 2395 scans in 666 individuals. 88 scans were followed by a secondary intervention in the follow-up, censored at 2 years, following scan. The point hazard ratio of this repeat analysis, Figure 19 (page 67), demonstrates the same distribution, at lower hazard ratios, as the initial analysis with baseline risk achieved by 0.5 years. 0.5 years was therefore assessed to be the appropriate timeframe to assess correlation between individual surveillance scan findings and secondary interventions.

2.4.4.2 Surveillance Scan Findings Correlation with Flow Related And Aneurysm Related Secondary Interventions

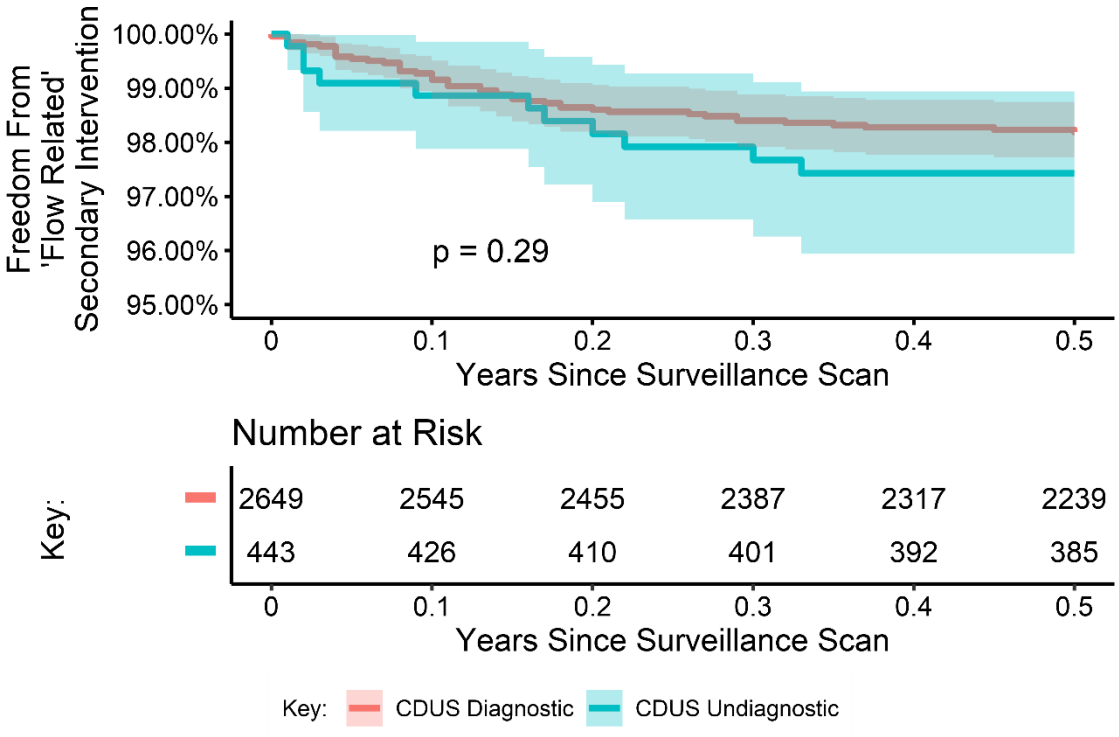
A total of 3092 surveillance visits in 756 individuals were assessed with 57 flow related and 49 aneurysm related secondary interventions occurring within 0.5 years. 72 CDUS scans had no AXR findings available, the time interval between AXR and CDUS had a Median of 0.00 years, Mean 0.06 years and inter-quartile range of 0.00 to 0.00 years. Confirming the great majority of CDUS and AXR scan findings combined for analysis occurred contemporaneously.

2.4.4.2.1 Colour Duplex Ultrasound Scan: Deemed Diagnostic

Achieving diagnostic views and findings was assessed in 3092 CDUS scans, 443 (14%) were reported as not fully diagnostic while the remaining 2649 (86%) were deemed to be diagnostic. No data was missing due to assessment methodology. A causal relationship could be hypothesised for flow related and aneurysm related secondary interventions.

The Kaplan-Meier plot for freedom from flow related secondary intervention, Figure 20(page 69), demonstrates no significant difference between the survival curves for diagnostic and undiagnostic CDUS, p=0.29. Cox proportional hazard model to the six months following scan, demonstrated those who had an undiagnostic CDUS had a non-significantly relationship with secondary interventions, hazard ratio 1.42 (95% CI 0.74 – 2.72, p=0.29).

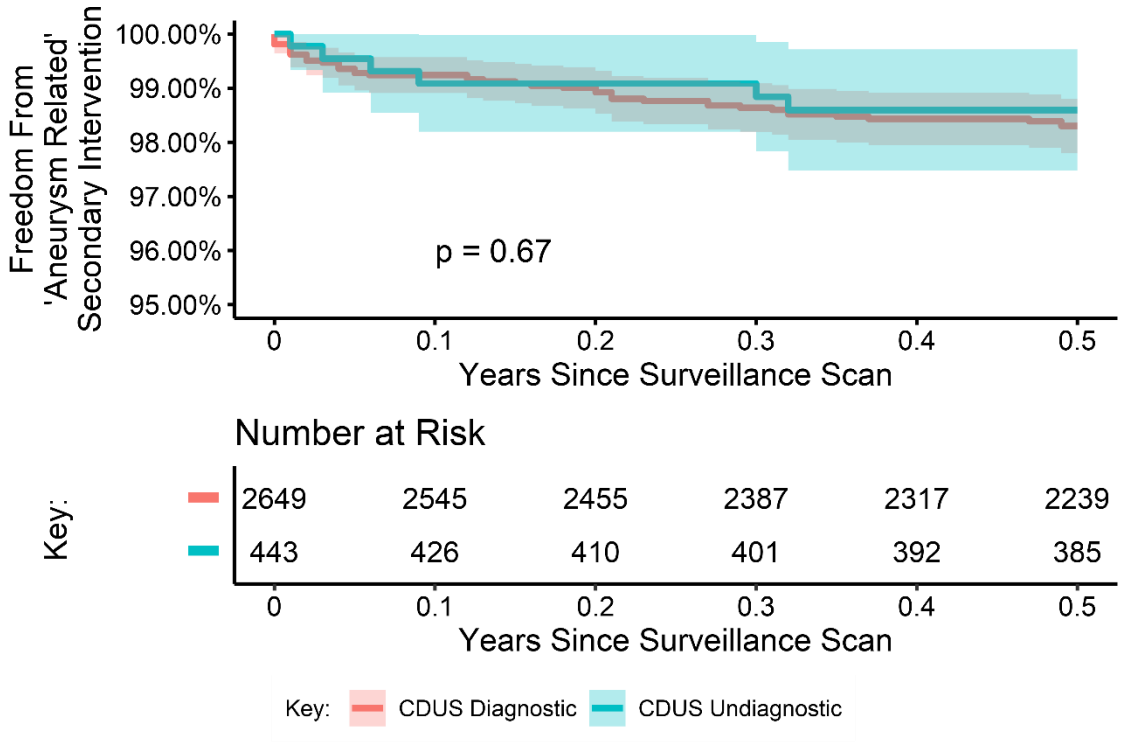
Figure 20: Freedom from Flow Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Diagnostic CDUS



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from flow related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if the current CDUS was undiagnostic. It demonstrates no significant difference in secondary interventions between the two groups.

The Kaplan-Meier plot for freedom from aneurysm related secondary intervention, Figure 21 (page 70), demonstrates almost exactly matching survival curves of diagnostic and undiagnostic CDUS, p=0.67. Cox proportional hazard model to the six months following scan, fails to demonstrate any perceivable relationship between diagnostic CDUS and freedom from aneurysm related secondary intervention, hazard ratio 0.83 (95% CI 0.52 – 2.79, p=0.67).

Figure 21: Freedom from aneurysm related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Diagnostic CDUS



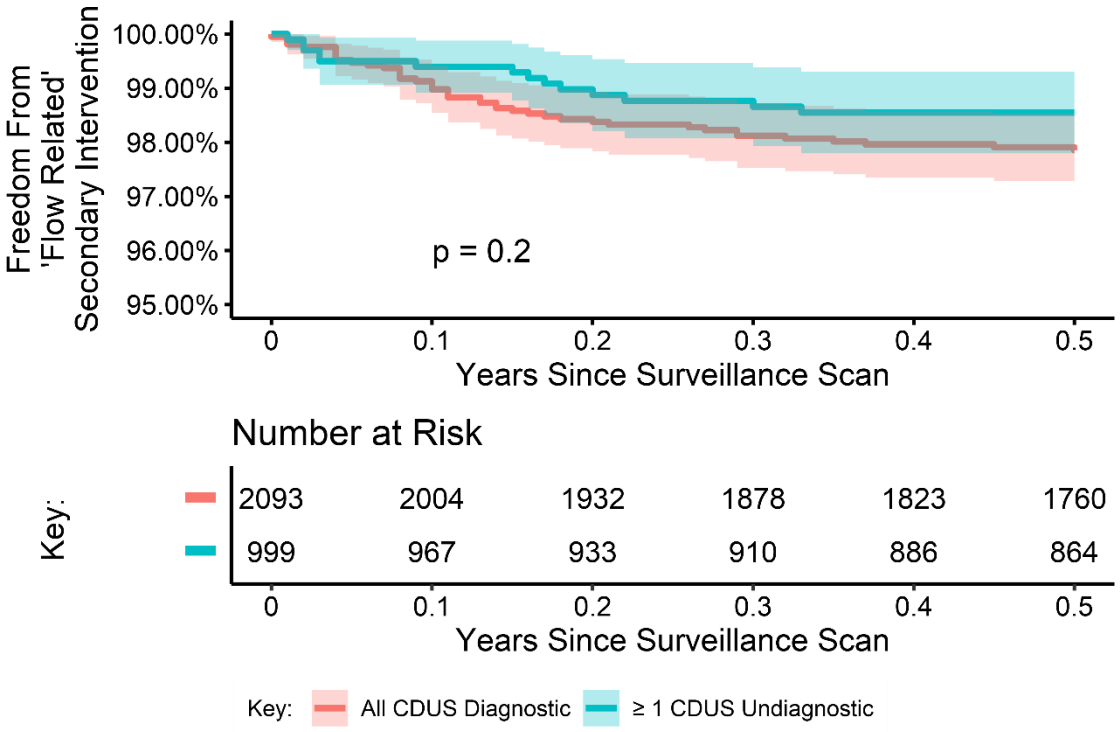
Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from aneurysm related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if the current CDUS was undiagnostic. It demonstrates no significant difference in secondary interventions between the two groups.

2.4.4.2.2 Colour Duplex Ultrasound Scan: Cumulative Deemed Diagnostic

A cumulative finding of diagnostic scans was calculated based on previous or current CDUS. This was measured at the point of 3092 current CDUS scans, 999 (32%) had 1 or more CDUSs that were not fully diagnostic while the remaining 2093 (68%) were deemed to have a full history of diagnostic CDUSs. No data was missing due to assessment methodology. A causal relationship could be hypothesised for flow related and aneurysm related secondary interventions.

The Kaplan-Meier plot for freedom from flow related secondary intervention, Figure 22 (page 71), demonstrates a similar generally linear freedom from secondary intervention between the groups that did not demonstrate statistical significance, p=0.20. Cox proportional hazard model to the six months following scan, demonstrated those who had an undiagnostic CDUS had a non-significant reduced risk of freedom from flow related secondary intervention, hazard ratio 0.67 (95% CI 0.37 – 1.22, p=0.20).

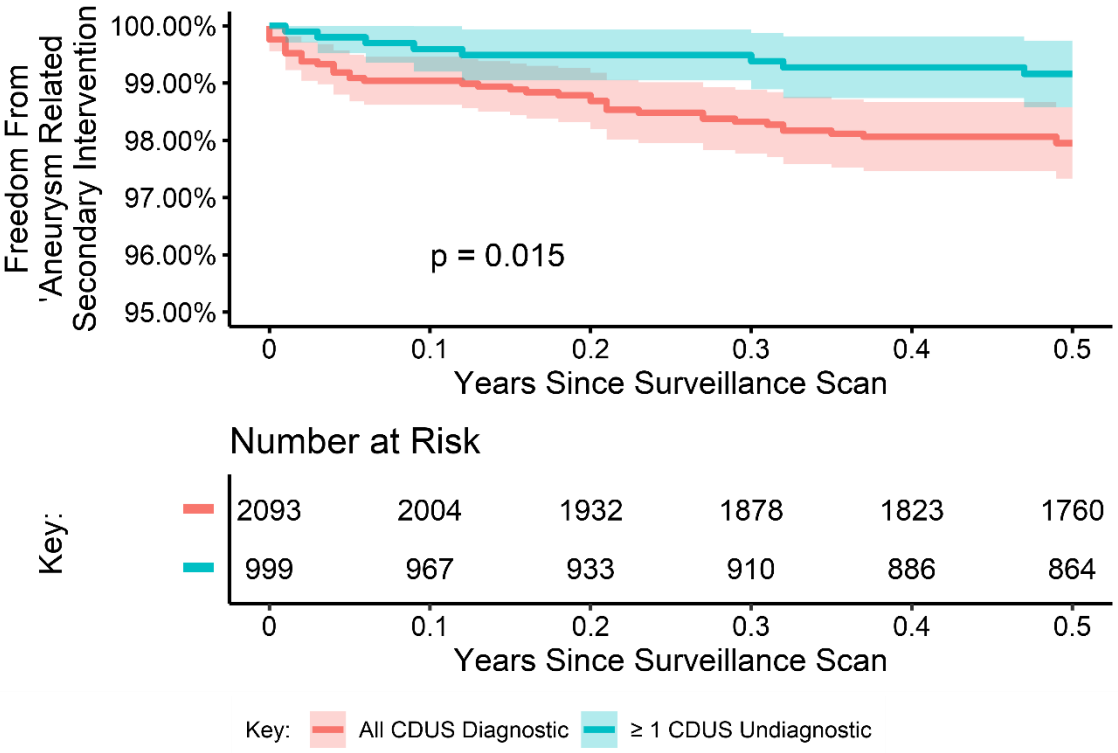
Figure 22: Freedom from flow related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Cumulative Diagnostic CDUSs



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from flow related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if the current or any previous CDUS was undiagnostic. It demonstrates no significant difference in secondary interventions between the two groups.

The Kaplan-Meier plot for freedom from aneurysm related secondary intervention, Figure 23 (page 72), demonstrates a initial and continuing divergence between diagnostic and undiagnostic groups. The group with all diagnostic scans were statistically significantly more at risk of requiring a secondary intervention, p=0.015. Cox proportional hazard model to the six months following scan, demonstrated those who had a history of all CDUS being diagnostic had significantly correlation with undergoing an aneurysm related secondary intervention, hazard ratio 0.40 (95% CI 0.19 – 0.85, p=0.02).

Figure 23: Freedom from Aneurysm Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Cumulative Diagnostic CDUS



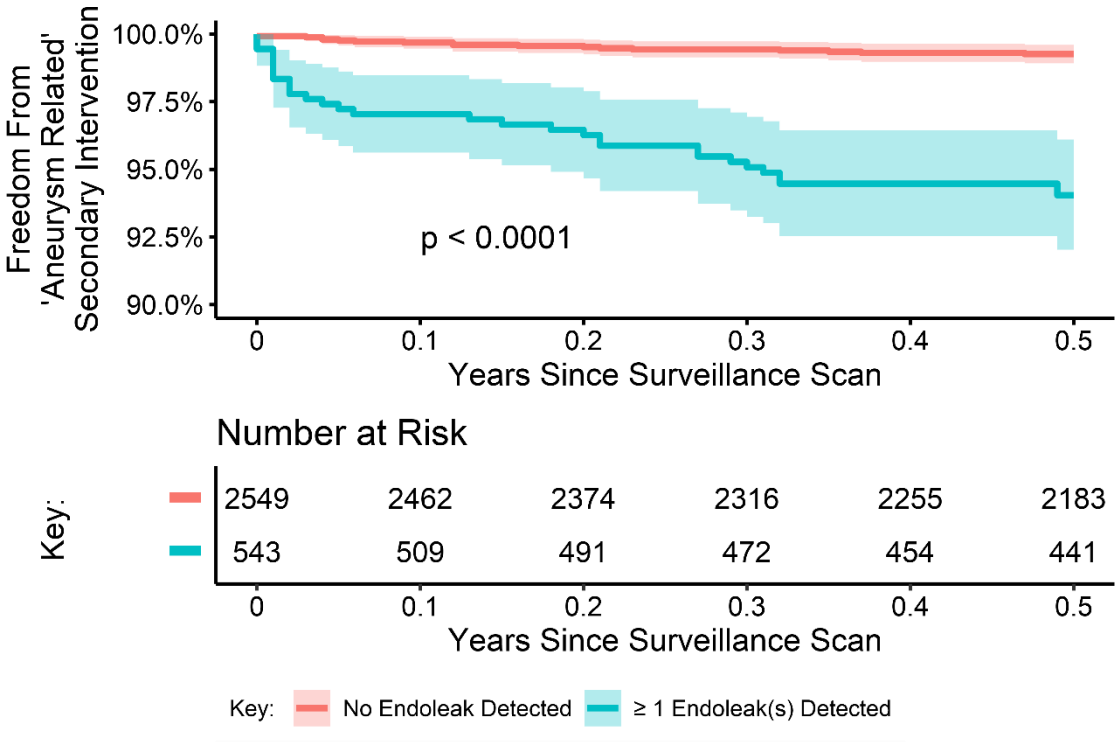
Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from aneurysm related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if the current or any previous CDUS was undiagnostic. It demonstrates if all previous CDUS were diagnostic secondary rates were higher than if any were undiagnostic.

2.4.4.2.3 Colour Duplex Ultrasound Scan: Any Endoleak

Assessment of presence / absence of any endoleak was assessed in 3092 CDUS scans, 543 (18%) demonstrated an endoleak while the remaining 2549 (82%) did not. No data was missing due to assessment methodology. A causal relationship could only be hypothesised to aneurysm related secondary interventions.

The Kaplan-Meier plot for freedom from aneurysm related secondary intervention, Figure 24 (page 73), demonstrates a marked immediate and continually increasing risk of aneurysm related secondary intervention following CDUS demonstrating any endoleak, virtually no secondary interventions were performed for those who had no endoleak detected, $p<0.0001$. Cox proportional hazard model to the six months following scan, demonstrated those who had an endoleak detected on CDUS had a significantly higher chance of undergoing an aneurysm related secondary intervention, hazard ratio 8.30 (95% CI 4.69 – 14.71, $p<0.0001$).

Figure 24: Freedom from Aneurysm Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Any Endoleak Detected



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from aneurysm related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if any endoleak was detected on the current CDUS. It demonstrates a significantly higher secondary intervention rate if an endoleak was diagnosed.

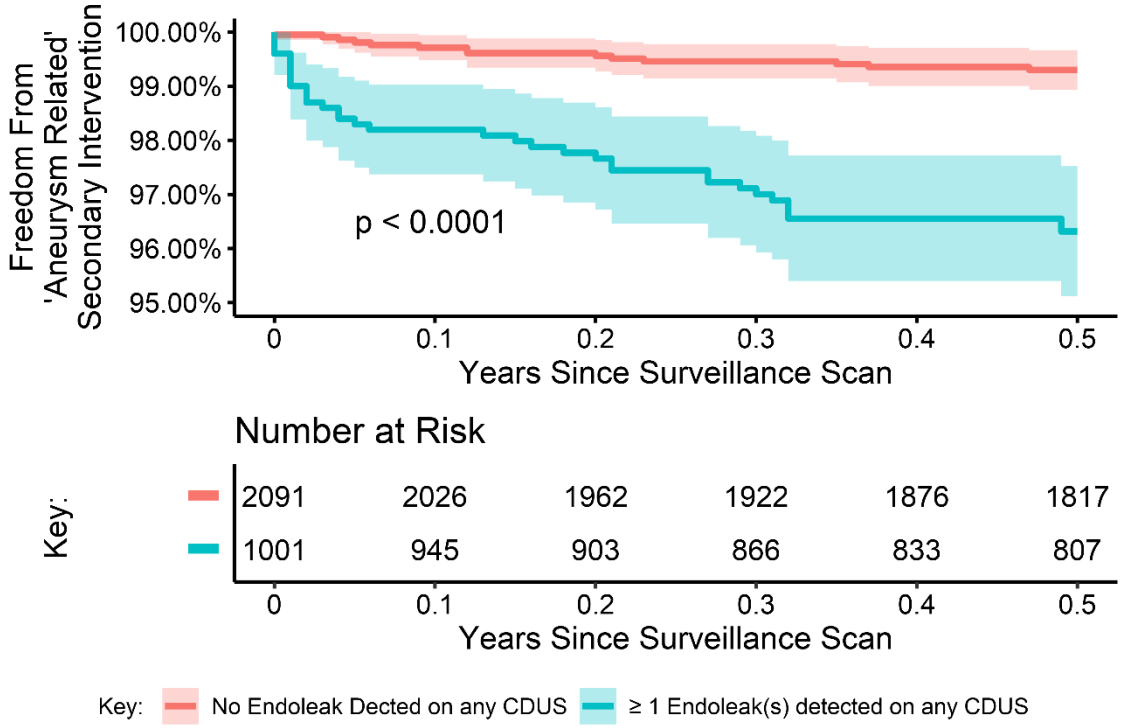
2.4.4.2.4 Colour Duplex Ultrasound Scan: Cumulative Any Endoleak

A cumulative finding of any endoleak was calculated based on presence on any previous or the current CDUS. This was measured at the point of 3092 current CDUS scans, 1001 (32%) had 1 or more CDUSs that detected an endoleak while the remaining 2091 (68%) did not have an endoleak detected. No data was missing due to the assessment methodology. A causal relationship could be inferred to only aneurysm related secondary interventions.

The Kaplan-Meier plot for freedom from aneurysm related secondary intervention, Figure 25 (page 74), demonstrates a marked immediate and continually increasing difference in the risk of aneurysm related secondary intervention following CDUS with at least 1 endoleak detected on any CDUS, with <1% risk of secondary interventions performed for those who had no endoleak detected, p<0.0001. Cox proportional hazard model to the six months following scan, demonstrated those who had an endoleak

detected on any CDUS had a significantly higher chance of undergoing an aneurysm related secondary intervention, hazard ratio 5.38 (95% CI 2.93 – 9.92, p<0.0001).

Figure 25: Freedom from Aneurysm Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Cumulative Any Endoleak on CDUS



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from aneurysm related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if any endoleak was detected on the current or any previous CDUS. It demonstrates a significantly higher secondary intervention rate if an endoleak was diagnosed on current or previous CDUS.

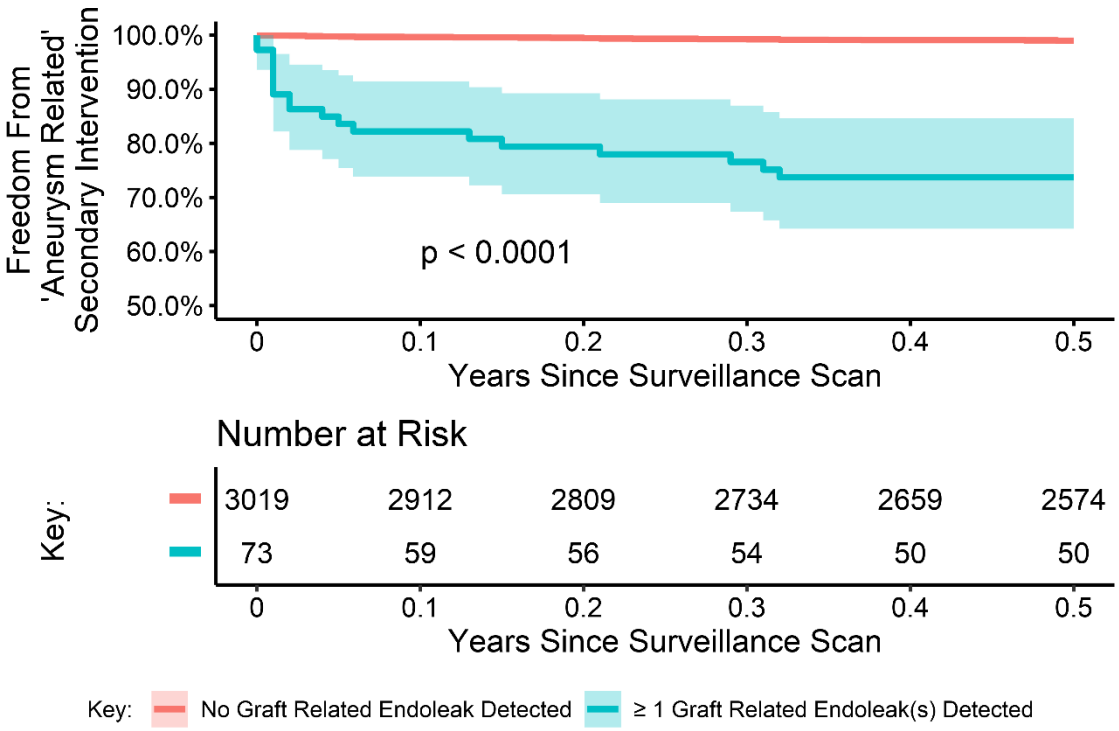
2.4.4.2.5 Colour Duplex Ultrasound Scan: Graft Related Endoleak

Assessment of presence / absence of a graft related endoleak was assessed on 3092 CDUS scans, 73 (2%) demonstrated an endoleak while the remaining 3019 (98%) did not. No data was missing due to assessment methodology. A causal relationship could only be hypothesised to aneurysm related secondary interventions.

The Kaplan-Meier plot for freedom from aneurysm related secondary intervention, Figure 26 (page 75), demonstrates immediate, continued and significant increased risk of those who had a graft related endoleak detected compared to those who did not, who had 0% risk of undergoing an aneurysm related secondary intervention, p<0.0001. Cox proportional hazard model to the six months following scan, demonstrated those who had a graft related endoleak detected on CDUS had a significantly higher chance of

undergoing a aneurysm related secondary intervention, hazard ratio 30.49 (95% CI 17.31 – 53.71, p<0.0001).

Figure 26: Freedom from Aneurysm Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Graft Related Endoleak Detected



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from aneurysm related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if a graft related endoleak was detected on the current CDUS. It demonstrates a significantly higher secondary intervention rate if a graft related endoleak was diagnosed on the current CDUS.

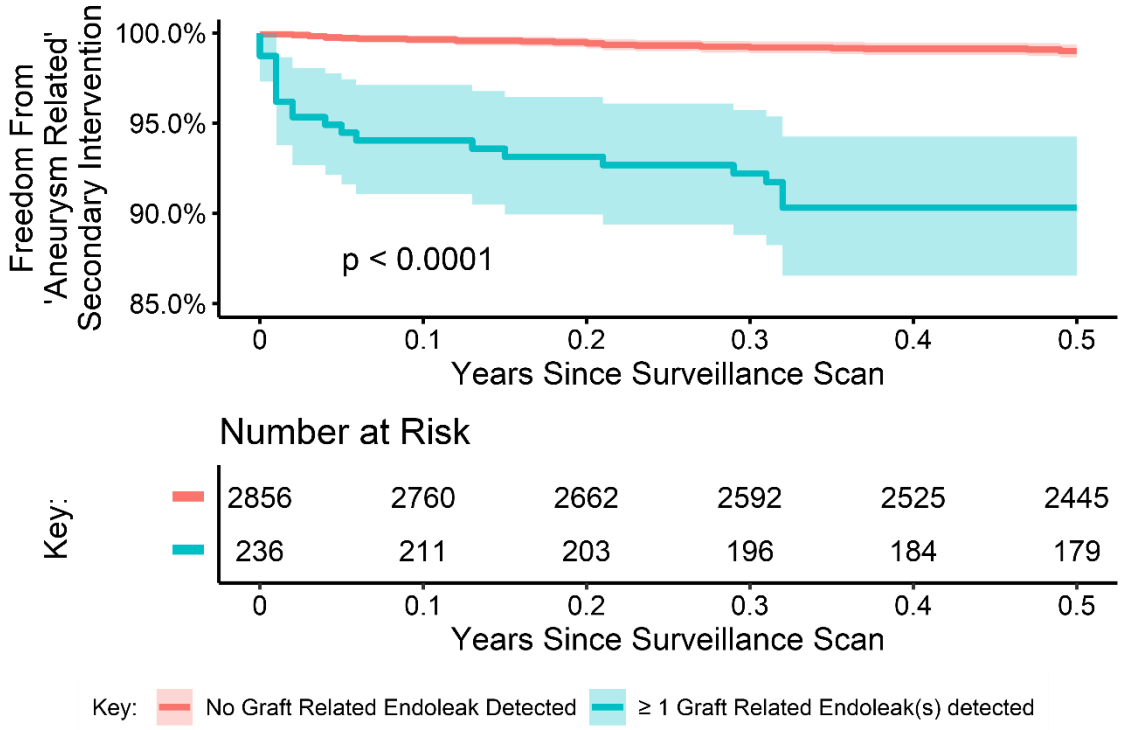
2.4.4.2.6 Colour Duplex Ultrasound Scan: Cumulative Graft Related Endoleak

A cumulative finding of graft related endoleak was calculated based on presence on any previous or the current CDUS. This was measured at the point of 3092 current CDUS scans, 236 (8%) had 1 or more CDUSs that detected a graft related endoleak while the remaining 2856 (92%) did not. No data was missing due to the assessment methodology. A causal relationship could be hypothesised to only aneurysm related secondary interventions.

The Kaplan-Meier plot for freedom from aneurysm related secondary intervention, Figure 27 (page 76), demonstrates early and continued divergence of risk for those with

a graft related endoleak compared to those without, p<0.0001. Cox proportional hazard model to the six months following scan, demonstrated those who had a graft related endoleak detected on any CDUS had a significantly higher chance on undergoing an aneurysm related secondary intervention, hazard ratio 10.52 (95% CI 6.04 – 18.32, p<0.0001).

Figure 27: Freedom from aneurysm related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Cumulative Graft Related Endoleak on CDUS



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from aneurysm related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if a graft related endoleak was detected on the current or any previous CDUS. It demonstrates a significantly higher secondary intervention rate if a graft related endoleak was diagnosed on the current or any previous CDUS.

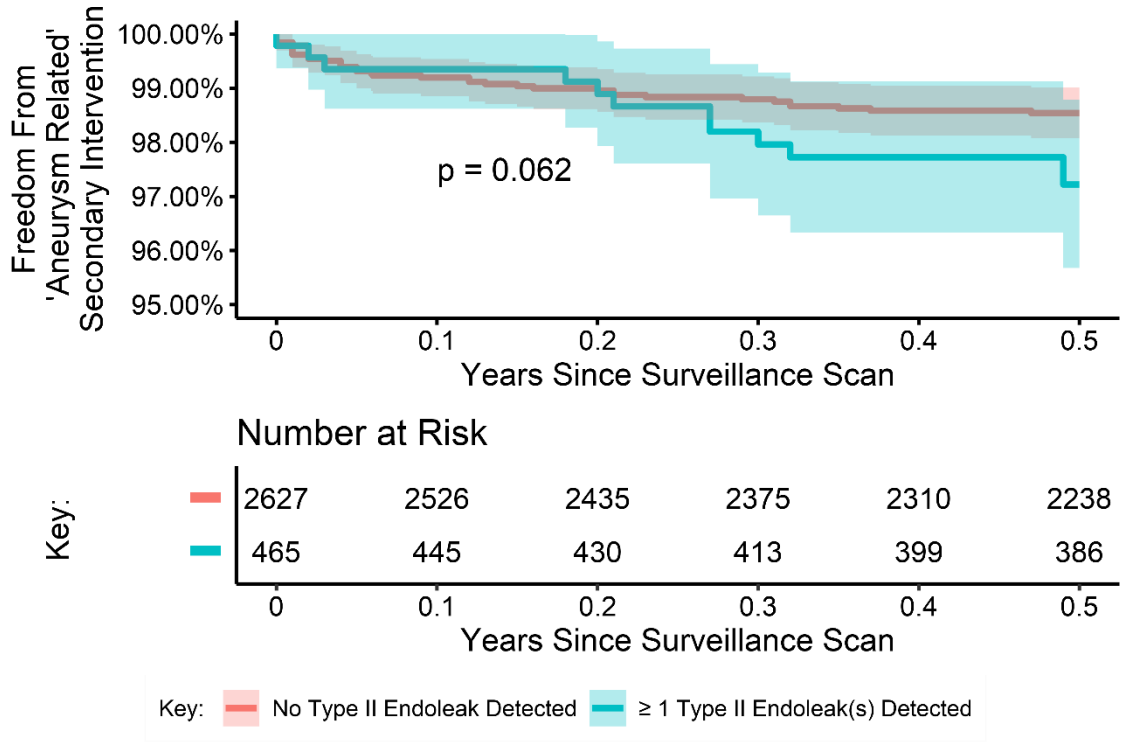
2.4.4.2.7 Colour Duplex Ultrasound Scan: Type II Related Endoleak

Assessment of presence / absence of a type II endoleak was assessed on 3092 CDUS scans, 465 (15%) demonstrated a type II endoleak while the remaining 2627 (85%) did not. No data was missing due to assessment methodology. A causal relationship could only be hypothesised to aneurysm related secondary interventions.

The Kaplan-Meier plot for freedom from aneurysm related secondary intervention, Figure 28 (page 77), demonstrates those with and without Type II endoleaks on current

CDUS had no statistical difference, p=0.062, but the curves are potentially diverging at the end of the 6 months. Cox proportional hazard model to the six months following scan, demonstrated presence or absence of a type II related endoleak detected on CDUS did not have a significant correlation with the chance of undergoing a aneurysm related secondary intervention, hazard ratio 1.84 (95% CI 0.97 – 3.50, p=0.07).

Figure 28: Freedom from aneurysm related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Type II Endoleak Detected



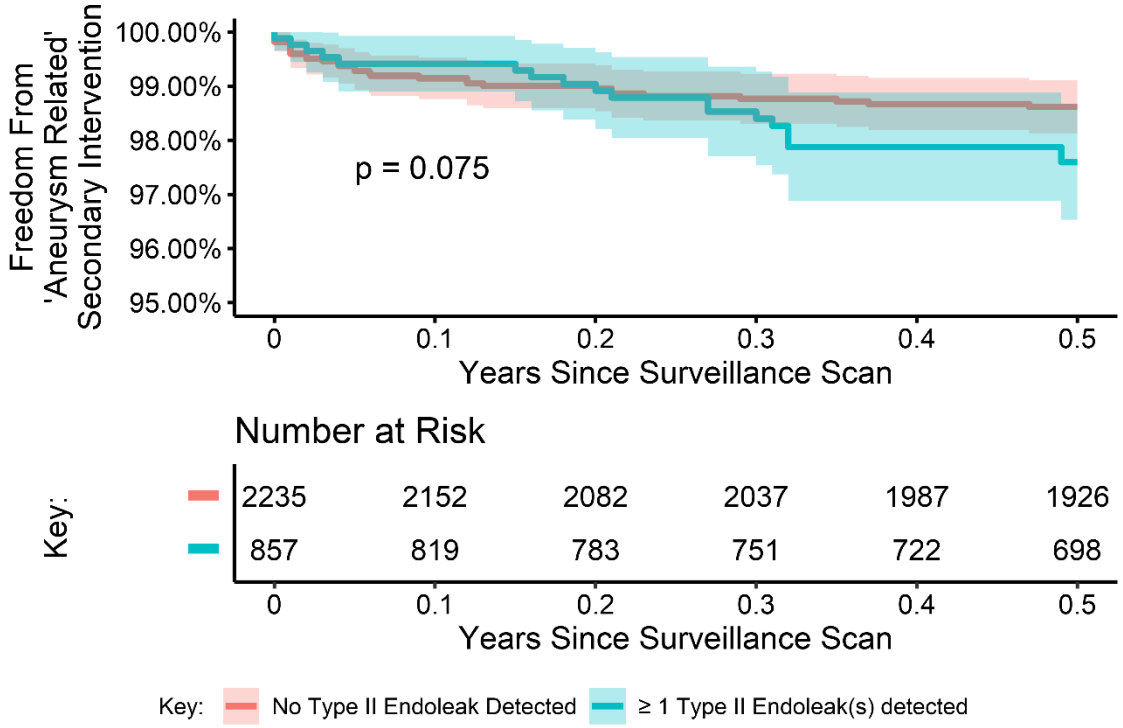
Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from aneurysm related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if a type II endoleak was detected on the current CDUS. It demonstrates no significant difference in secondary intervention rate if a type II endoleak was diagnosed on the current CDUS.

2.4.4.2.8 Colour Duplex Ultrasound Scan: Cumulative Type II Related Endoleak

A cumulative finding of type II endoleak was calculated based on presence on any previous or the current CDUS. This was measured at the point of 3092 current CDUS scans, 857 (28%) had 1 or more CDUSs that detected a type II endoleak while the remaining 2235 (72%) did not. No data was missing due to the assessment methodology. A causal relationship could be hypothesised to only aneurysm related secondary interventions.

The Kaplan-Meier plot for freedom from aneurysm related secondary intervention, Figure 29 (page 78), demonstrates those with or without Type II endoleaks on any CDUS had no discernible difference in risk, p=0.075. Cox proportional hazard model to the six months following scan, demonstrated that the presence absence of a type II endoleak detected on any CDUS had no significantly relationship to undergoing an aneurysm related secondary intervention, hazard ratio 1.68 (95% CI 0.95 – 2.95, p=0.08).

Figure 29: Freedom from aneurysm Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Cumulative Type II Endoleak on CDUS



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from aneurysm related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if a type II endoleak was detected on the current or any previous CDUS. It demonstrates no significant difference in secondary intervention rate if a type II endoleak was diagnosed on the current or any previous CDUS.

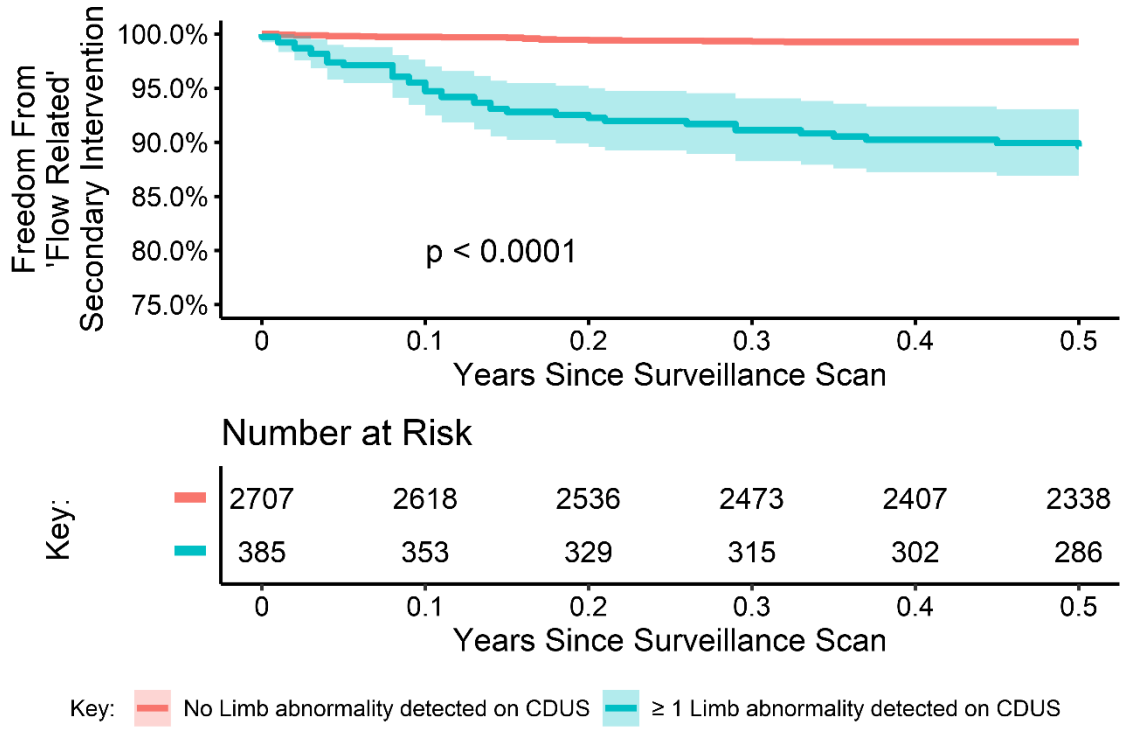
2.4.4.2.9 Colour Duplex Ultrasound Scan: Limb Abnormality

Assessment of EVAR limbs is part of the standard operating procedure for a CDUS surveillance scan post EVAR. Continuous variables (such as flow velocities) were only reported if a gross abnormality was observed by the operator. As such these continuous variables have biases introduced and only the initial binary assessment of any pathology (present / absent) is suitable for analysis. 3092 CDUS scans were assessed, 385 (12%)

had limb abnormalities detected on that scan while the remaining 2707 (88%) did not. No data was missing due to assessment methodology. Causal relationship could only be inferred to flow related secondary interventions.

The Kaplan-Meier plot for freedom from flow related secondary intervention Figure 30 (page 79), demonstrates approximately linear increasing in risk for those with a limb abnormality with almost no risk by 0.5 years for those without, p<0.0001. Cox proportional hazard model to the six months following scan, demonstrated those who had a limb abnormality detected had significantly less chance of remaining free from flow related secondary intervention, hazard ratio 14.935 (95% CI 8.69 – 25.70, p<0.0001).

Figure 30: Freedom from Flow Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Detection of Limb Abnormality on CDUS



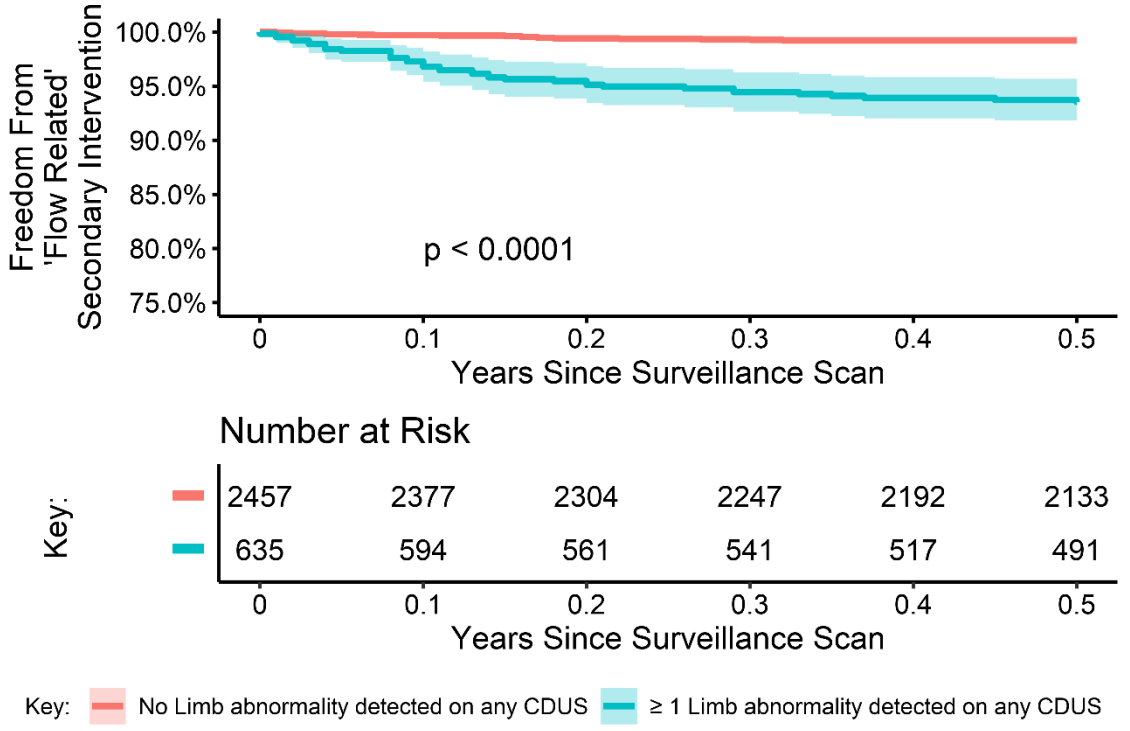
Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from flow related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if a limb abnormality was detected on the current CDUS. It demonstrates a significant increase in secondary intervention rate if a limb abnormality was diagnosed on the current CDUS.

2.4.4.2.10 Colour Duplex Ultrasound Scan: Cumulative Limb Findings

A cumulative finding of any limb abnormality detected on previous or current CDUS was calculated. 3092 CDUS scans were assessed, 635 (21%) had limb abnormalities detected on the current or previous scan while the remaining 2457 (79%) did not.

The Kaplan-Meier plot for freedom from flow related secondary intervention, Figure 31 (page 80), demonstrates approximately linear increasing in risk for those with a limb abnormality with almost no risk by 0.5 years for those without, p<0.0001. Cox proportional hazard model to the six months following scan demonstrated those who had a limb abnormality detected at any time had significantly less chance of remaining free from flow related secondary intervention, hazard ratio 8.71 (95% CI 5.02 – 15.09, p<0.0001).

Figure 31: Freedom from Flow Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Detection of Limb Abnormality on Current or Previous CDUS



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from flow related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if a limb abnormality was detected on the current or any previous CDUS. It demonstrates a significant increase in secondary intervention rate if a limb abnormality was diagnosed on the current or any previous CDUS.

2.4.4.2.11 Colour Duplex Ultrasound Scan: AAA Size (mm)

AAA size was assessed as part of 3092 CDUS scans, 125 (4%) did not have a recorded size measurement. Median and mean size were 56 and 57mm respectively, inter-quartile range was 45 to 65mm. Causal relationship could be hypothesised for both flow related, and aneurysm related secondary interventions.

Cox proportional hazard modelling with a variable for missingness showed that the missingness variable was statistically significant for both flow related, and aneurysm related secondary interventions, p=0.004 and p=0.0002 respectively. As such the data was assessed to be NMAR.

Cox proportional hazard models on the multiple imputed data to the six months following CDUS showed absolute aneurysm size had no significant relationship with flow related secondary intervention, hazard ratio 1.01 (95% CI 0.99 – 1.02, p=0.41), per 1mm size increase. Cox proportional hazard models on the multiple imputed data to the six months following CDUS showed absolute aneurysm size had a highly significant relationship with aneurysm related secondary intervention, hazard ratio 1.04 (95% CI 1.03 – 1.05, p<0.0001), per 1mm size increase.

2.4.4.2.12 Colour Duplex Ultrasound Scan: Maximum Growth

A variable was calculated to show the absolute growth between the smallest size measured on any surveillance scan and the current size. This difference could only be a positive size in millimetres or 0 (if current scan were the smallest). If no other measurements were available as this was the first surveillance scan in the observational period this was also recorded as 0. In total 3092 CDUS scans were assessed, 125 (4%) did not have a recorded size measurement. Median and Mean maximum growth were 0 and 2.2mm respectively. Inter-quartile range was 0 to 2mm. Causal relationship could be inferred for both flow related and aneurysm related secondary interventions.

Cox proportional hazard modelling with a variable for missingness showed that the missingness variable was statistically significant for flow related but not aneurysm related secondary interventions, p=0.002 and p=0.23 respectively. As such the data was assessed to be NMAR for the flow related analysis.

Cox proportional hazard models on the multiple imputed data to the six months following CDUS showed maximum aneurysm growth had significant inverse relationship with flow related secondary intervention, hazard ratio 0.81 (95% CI 0.67 – 0.98, p=0.03), per 1mm size increase. Cox proportional hazard models on available data

to the six months following CDUS showed maximum aneurysm growth had significant direct relationship with aneurysm related secondary interventions, hazard ratio 1.06 (95% CI 1.04 – 1.09, p<0.0001), per 1mm size increase.

2.4.4.2.13 Colour Duplex Ultrasound Scan: Recent Growth

A variable was calculated to show the recent growth between the size measured on the previous surveillance scan and the size on the current scan. The previous scan must have been over 3 months ago. 3092 CDUS scans were assessed, 988 (32%) did not have the necessary size measurements to calculate a recent growth, the majority of which were scan in the first 3 months of surveillance. Median and Mean growth rates were -1 and -1.4mm respectively. Inter-quartile range was -4 to +2mm. Causal relationship could be inferred for both flow related and aneurysm related secondary interventions.

Cox proportional hazard modelling with a variable for missingness showed that the missingness variable was statistically significant for both flow related and aneurysm related secondary interventions, p<0.0001 and p=0.004 respectively, as such the data was assessed to be NMAR.

Cox proportional hazard models on the multiple imputation data to the six months following CDUS showed recent growth had no significant relationship with flow related secondary intervention, hazard ratio 1.03 (95% CI 0.94 – 1.12, p=0.54), per 1mm size increase. Cox proportional hazard models on the multiple imputed data to the six months following CDUS showed absolute recent growth had a highly significant relationship with aneurysm related secondary intervention, hazard ratio 1.11 (95% CI 1.07 – 1.16, p<0.0001), per 1mm size increase.

2.4.4.2.14 Colour Duplex Ultrasound Scan: Recent Growth Rate

A variable was calculated to show the recent growth between the size measured on the previous surveillance scan and the current size divided by the time (in years) since the previous scan, which must have been over 3 months ago. 3092 CDUS scans were assessed, 988 (32%) did not have sufficient size measurements to calculate a recent growth, the majority of which were scan in the first 3 months of surveillance. Median and mean growth rates were -1.00 and -1.44 mm/year respectively. Inter-quartile range was -4.00 to +2.00 mm/year. Causal relationships could be hypothesised for both flow related and aneurysm related secondary interventions.

Cox proportional hazard modelling with a variable for missingness showed that the missingness variable was statistically significant in assessment of flow related and aneurysm related secondary interventions, $p<0.0001$ and $p=0.004$ respectively. As such these data were assessed to be NMAR

Cox proportional hazard models on the multiple imputation data to the six months following CDUS showed recent growth rate had no significant relationship with flow related secondary intervention, hazard ratio 1.01 (95% CI 0.95 – 1.07, $p=0.82$), per 1mm/year size increase. Cox proportional hazard models on the multiple imputed data to the six months following CDUS showed absolute recent growth had a highly significant relationship with aneurysm related secondary intervention, hazard ratio 1.06 (95% CI 1.04 – 1.09, $p<0.0001$), per 1mm/year size increase.

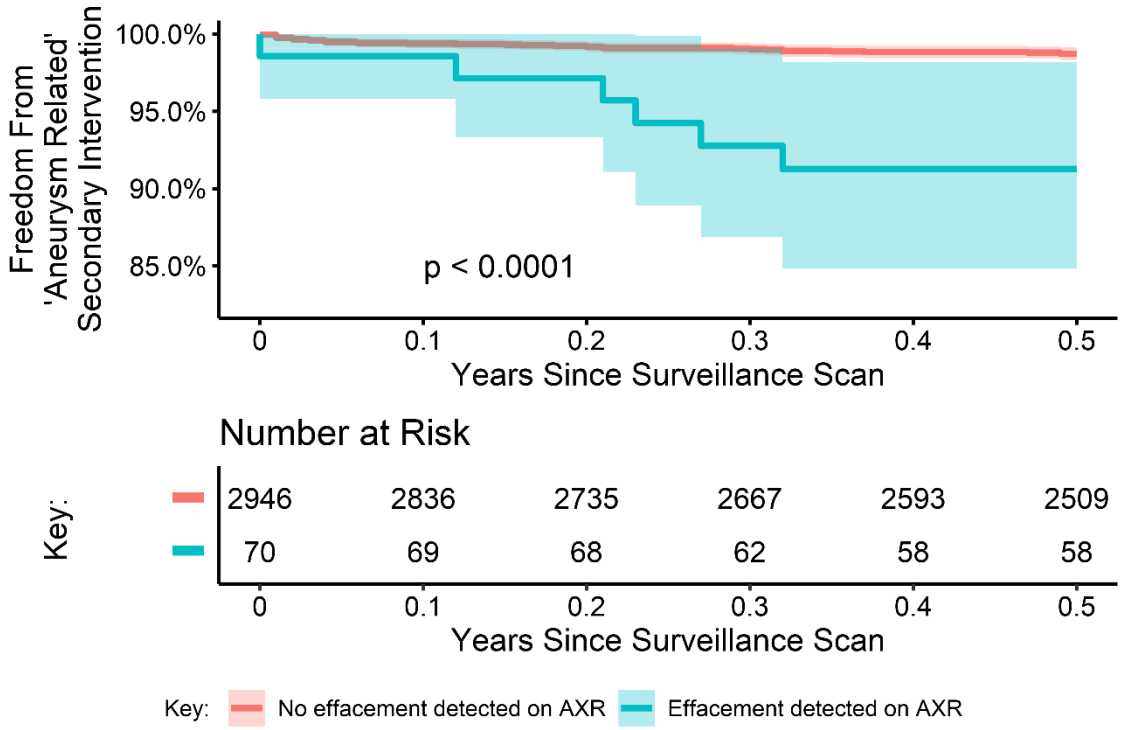
2.4.4.2.15 Plain Abdominal Radiograph: Effacement Finding

A True / False finding of effacement was created for each AXR. All AXR findings were assessed in relation to the most recent AXR for each CDUS performed. 3092 CDUS scans were assessed, 76 (2%) had had no AXR findings available. 70 (2%) demonstrated findings indicative of effacement, 2946 (95%) did not. Causal inference could only be hypothesised for aneurysm related secondary interventions.

The Kaplan-Meier plot for freedom from aneurysm related secondary intervention, Figure 32 (page 84), demonstrates an initially similar risk in effacement and no effacement group but at 0.2 years those with effacement have an increasing risk of secondary intervention, $p<0.0001$.

Those with missing data had a similar rate (9%) of aneurysm related secondary intervention as those with effacement (9%) but much higher than those with no effacement (1%). These data were therefore assessed as being NMAR. Cox proportional hazard model, on multiple imputed data, to the six months following scan, demonstrated those who had effacement detected had significantly less chance of remaining free from aneurysm related secondary intervention, hazard ratio 7.03 (95% CI 3.00 – 16.46, $p<0.0001$).

Figure 32: Freedom from Aneurysm Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Detection of Effacement on AXR



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from aneurysm related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if effacement was detected on the most recent AXR. It demonstrates a significant increase in secondary intervention rate if effacement was detected on the most recent AXR.

2.4.4.2.16 Plain Abdominal Radiograph: Cumulative Effacement Finding

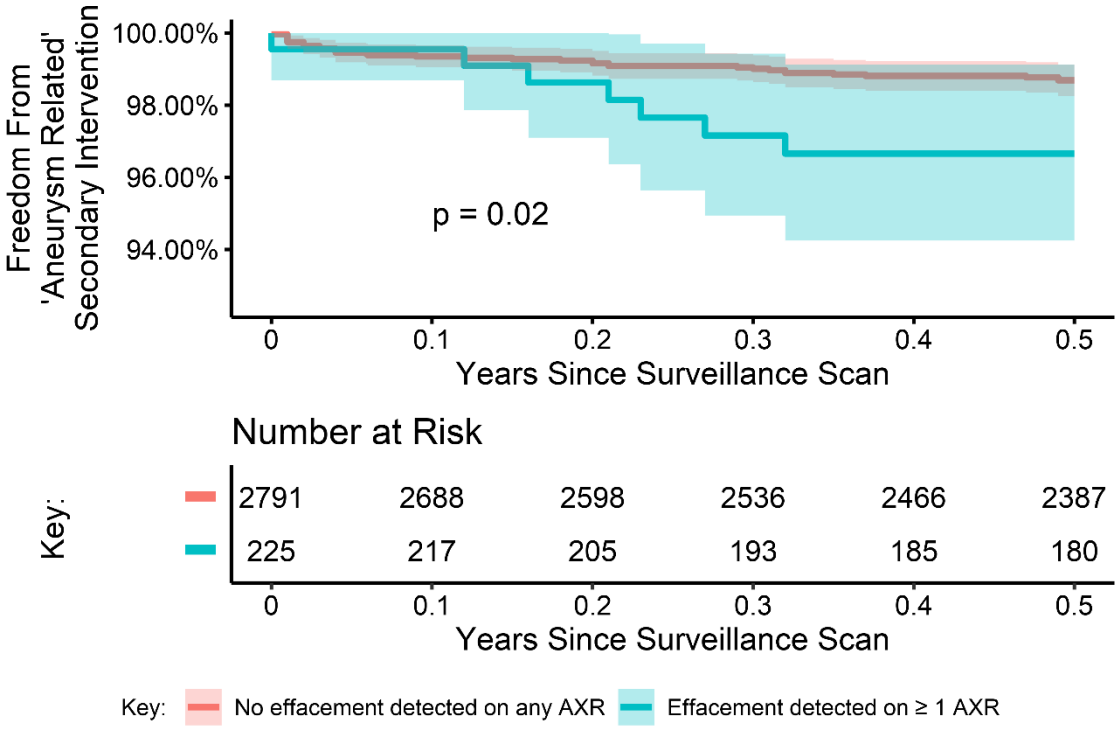
A True / False finding of effacement on current or any previous AXR was created for each CDUS visit. 3092 CDUS scans were assessed, 76 (2%) had had no AXR findings available. 225 (7%) demonstrated effacement currently or in the past, 2791 (90%) did not. Causal inference could only be hypothesised for aneurysm related secondary interventions.

The Kaplan-Meier plot for freedom from aneurysm related secondary intervention, Figure 33 (page 85), demonstrates an initially similar risk in effacement and no effacement on any AXR groups, but at 0.15 years those with effacement have an increasing risk of secondary intervention, p=0.02.

Those with missing data had a much higher rate (9%) of aneurysm related secondary intervention than those with effacement (3%) and no cumulative effacement (1%). These data were therefore assessed as being NMAR. Cox proportional hazard model, on

multiple imputed data, to the six months following scan, demonstrated those who had effacement detected on any AXR had significantly less chance of remaining free from aneurysm related secondary intervention, hazard ratio 2.54 (95% CI 1.14 – 5.64, p=0.02).

Figure 33: Freedom from Aneurysm Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Detection of Effacement on any AXR



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from aneurysm related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if effacement was detected on the most recent or any previous AXR. It demonstrates a significant increase in secondary intervention rate if effacement was detected on the most recent or any previous AXR.

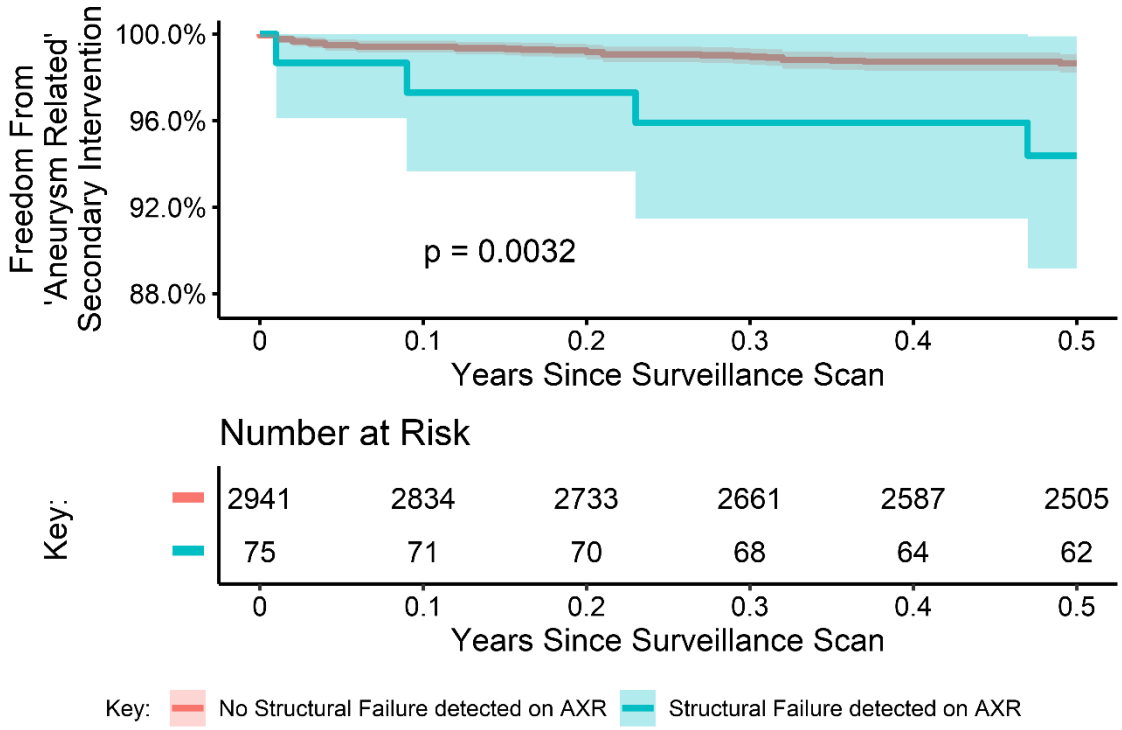
2.4.4.2.17 Plain Abdominal Radiograph: Structural Failure Finding

A True / False finding of structural failure was created for each AXR. All AXR findings were assess in relation to the most recent AXR for each CDUS performed. 3092 CDUS scans were assessed, 76 (2%) had had no AXR findings available. 75 (2%) demonstrated structural failure, 2941 (95%) did not. Causal inference could only be hypothesised for aneurysm related secondary interventions.

The Kaplan-Meier plot for freedom from aneurysm related secondary interventions, Figure 34 (page 86), shows slow but consistent increase in risk for those with structural failure detected, compared to a relatively stable risk for those without structural failure, p=0.0032.

Those with missing data had a much higher rate (9%) of secondary intervention than those with structural failure (5%) and no structural failure (1%) respectively. These data were therefore assessed as being NMAR. Cox proportional hazard model, on multiple imputed data, to the six months following scan, demonstrated those who had structural failure detected had significantly less chance of remaining free from aneurysm related secondary intervention, hazard ratio 4.16 (95% CI 1.51 – 11.48, p=0.006).

Figure 34: Freedom from Aneurysm Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Detection of Structural Failure on AXR



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from aneurysm related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if a structural failure was detected on the most recent AXR. It demonstrates a significant increase in secondary intervention rate if a structural failure was detected on the most recent AXR.

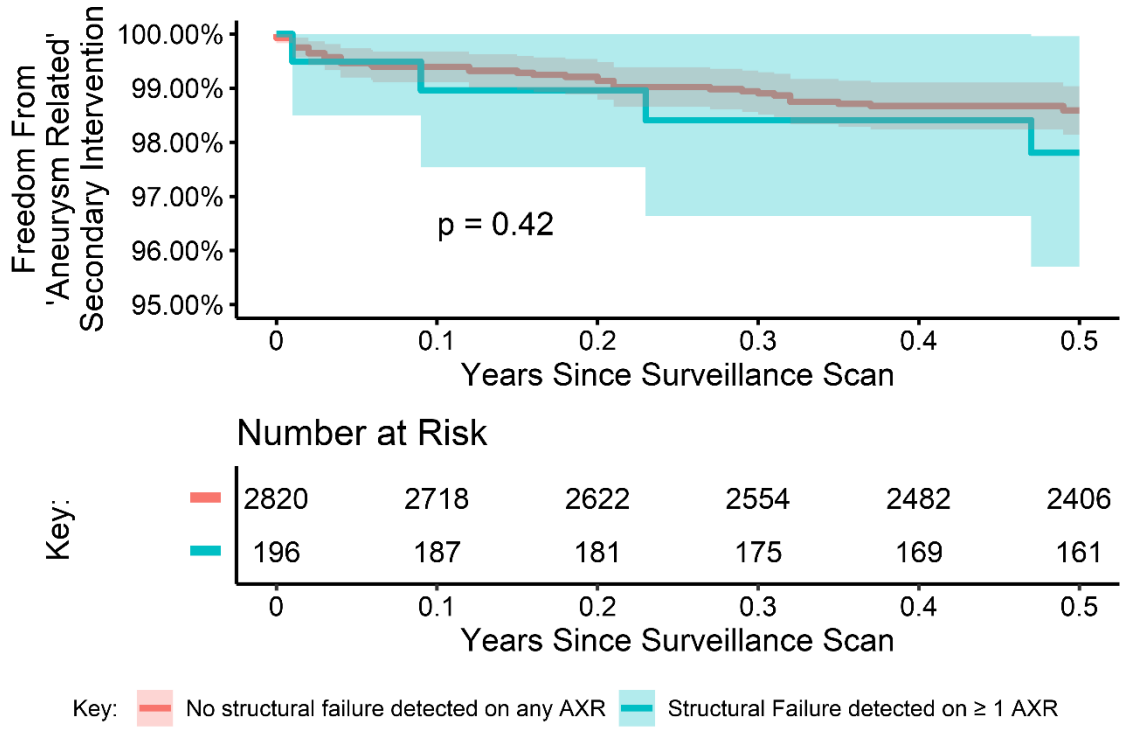
2.4.4.2.18 Plain Abdominal Radiograph: Cumulative Structural Failure Finding

A True / False finding of a structural failure on current or any previous AXR was created for each CDUS visit. 3092 CDUS scans were assessed, 76 (2%) had had no AXR findings available. 196 (6%) demonstrated effacement currently or in the past, 2820 (91%) did not. Causal inference could only be hypothesised for aneurysm related secondary interventions.

The Kaplan-Meier plot for freedom from aneurysm related secondary interventions, Figure 35 (page 87), shows no discernible difference between the groups, p=0.42.

Those with missing data had a much higher rate of aneurysm related secondary intervention (9%) than those with cumulative findings of structural failure (2%) and no cumulative finding of structural failure (1%). These data were therefore assessed as being NMAR. Cox proportional hazard model, on multiple imputed data, to the six months following scan, demonstrated that a structural failure detected on any AXR had no relationship to remaining free from aneurysm related secondary intervention, hazard ratio 1.53 (95% CI 0.55– 4.21, p=0.42).

Figure 35: Freedom from Aneurysm Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Detection of Structural Failure on any AXR



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from aneurysm related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if a structural failure was detected on the most recent or any previous AXR. It demonstrates no significant difference in secondary intervention rates if a structural failure was detected on the most recent or any previous AXR.

2.4.4.2.19 Plain Abdominal Radiograph: Limb Abnormality Findings

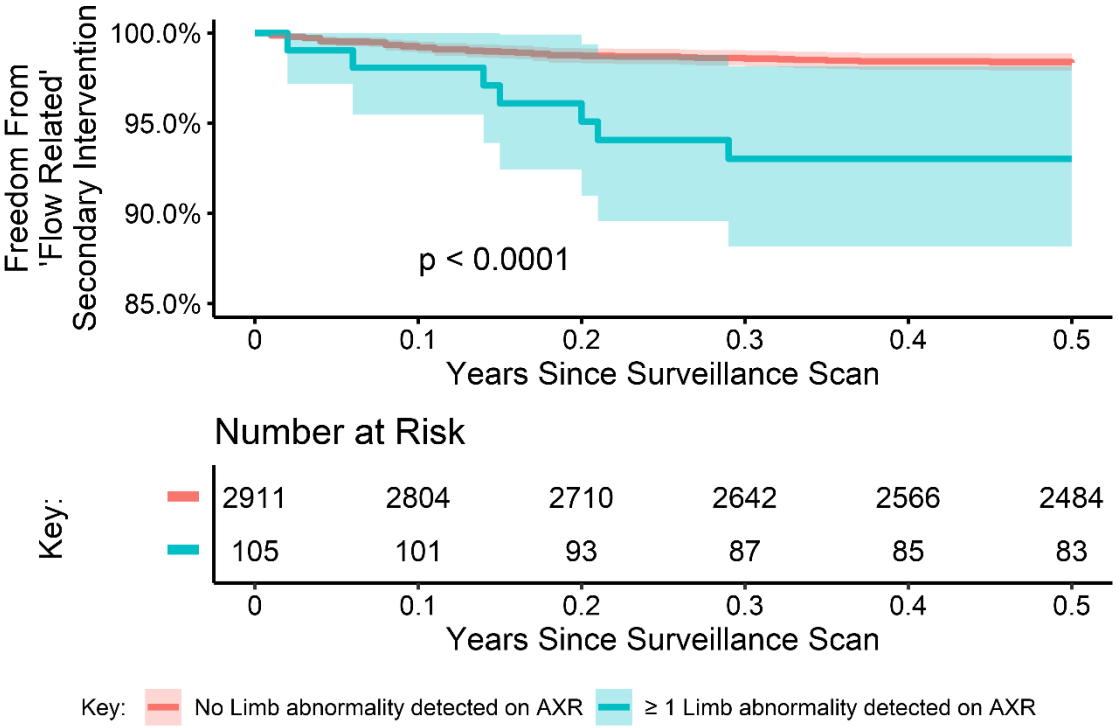
AXR variables were assessed in relation to the corresponding 3092 CDUS scans, contemporary or previous AXRs were available for all but 76 of these scans. Therefore,

no data on limb abnormalities on AXR was available for 2% of CDUS surveillance visits under investigation. 105 (3%) of visits had limb abnormalities detected on AXR while the remaining 2911 (94%) did not. Causal inference could only be hypothesised for flow related secondary interventions.

The Kaplan-Meier plot for freedom from flow related secondary interventions, Figure 36 (page 88), shows slow but consistent increase in risk for those with limb abnormality, compared to a relatively stable risk for those without limb abnormality, p<0.0001.

Those with missing data had a 5% rate of flow related secondary intervention compared to those with findings of limb abnormality (7%) and no limb abnormality (2%). These data were therefore assessed as being NMAR. Cox proportional hazard models on the multiple imputed data to the six months following scan demonstrated those who had a limb abnormality detected had significantly less chance of remaining free from flow related secondary intervention, hazard ratio 4.32 (95% CI 1.98 – 9.46, p=0.0003).

Figure 36: Freedom from Flow Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Detection of Limb Abnormality on AXR



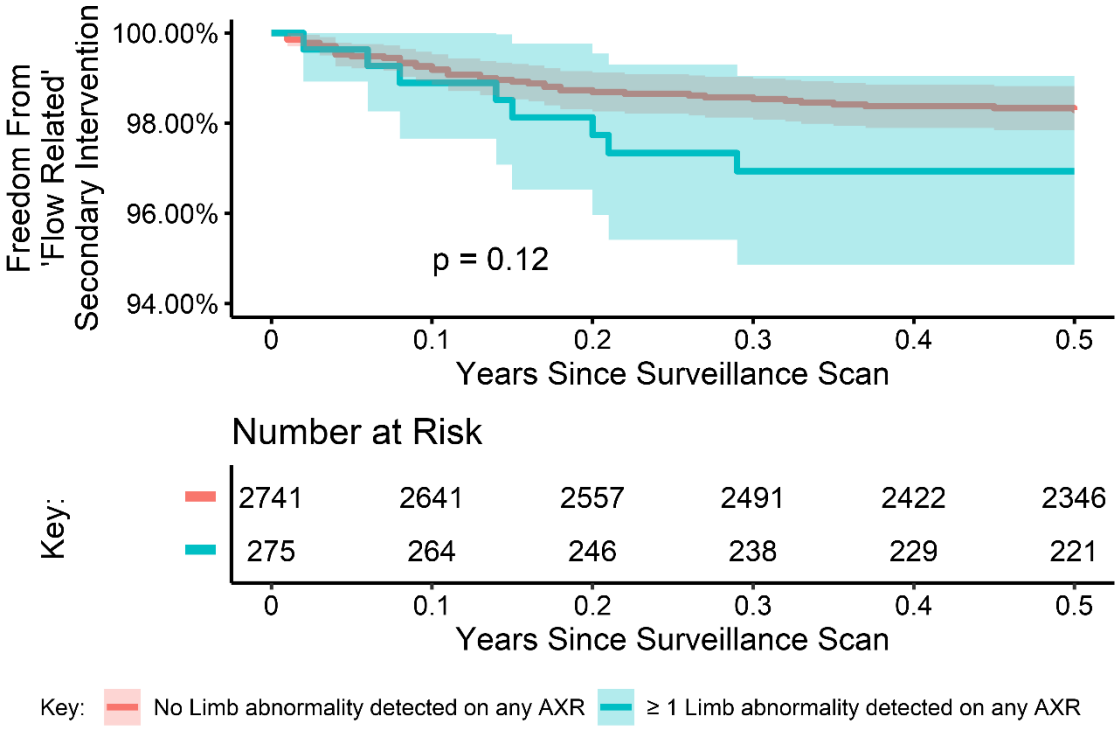
Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from flow related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if limb kink was detected on the most recent AXR. It demonstrates a significant increase in secondary intervention rates if a limb kink was detected on the most recent AXR.

2.4.4.2.20 Plain Abdominal Radiograph: Cumulative Limb Abnormality Findings

A cumulative finding of any limb abnormality detected on previous or current AXR was calculated. This variable was assessed in relation to the corresponding 3092 CDUS scans, responses were available for all but 76 of these scans. Therefore, no data on cumulative limb abnormalities on AXR was available for 2% of CDUS surveillance visits under investigation. 275(9%) of visits had limb abnormalities detected on any AXR while the remaining 2741 (89%%) did not. Causal inference could only be hypothesised for flow related secondary interventions.

The Kaplan-Meier plot for freedom from flow related secondary interventions, Figure 37 (page 89), shows slow but consistent increase in risk for those with limb abnormality on any AXR, compared to an initially increasing risk which then stabilises out at approximately 0.2 years for those without limb abnormality, p=0.12.

Figure 37: Freedom from Flow Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Detection of Limb Abnormality on Current or Previous AXR



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from flow related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if limb kink was detected on the most recent or any previous AXR. It demonstrates no significant difference in secondary intervention rates if a limb kink was detected on the most recent or any previous AXR.

Those with missing data had a 5% rate of flow related secondary intervention compared to those with findings of limb abnormality and no limb abnormality, 3% and 2% respectively. These data were therefore assessed as being NMAR. Cox proportional hazard models on the multiple imputed data to the six months following scan showed a limb abnormality detected on the current or any previous AXR had no significant relationship with flow related secondary intervention, hazard ratio 1.80 (95% CI 0.86 – 3.77, p=0.13).

2.4.4.2.21 Plain Abdominal Radiograph: Migration Findings

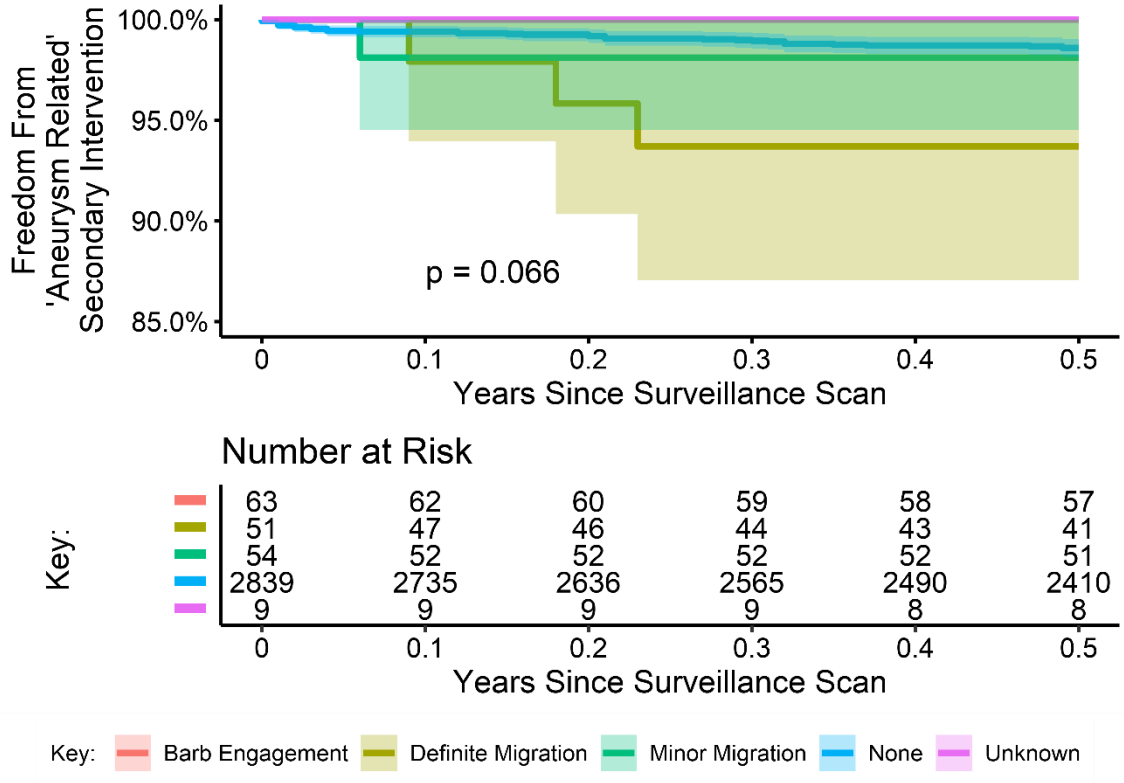
AXR variables were assessed in relation to the corresponding 3092 CDUS scans, contemporary or previous AXRs were available for all but 76 of these scans. Therefore, no data on limb abnormalities on AXR was available for 2% of CDUS surveillance visits under investigation. 2839 (92%) had no migration detected while 177 (6%) did have migration identified. Migration was subcategorised: barb engagement (63), minor migration (54), definite migration (51) and undefined (9). Causal inference could only be hypothesised for aneurysm related secondary interventions.

Kaplan-Meier plot, Figure 38 (page 91), comparing the various findings demonstrated there was only a significant difference between definite migration and the other findings. No other individual or group of findings demonstrated significance in freedom from secondary intervention. As such all other findings were grouped together to allow the calculation of hazard ratios and a cumulative finding to be investigated.

The Kaplan-Meier plot for freedom from aneurysm related secondary interventions, Figure 39 (page 92), shows steady but consistent increase in risk for those with definite migration on AXR, compared to little to no risk for those without definite migration, p=0.0053.

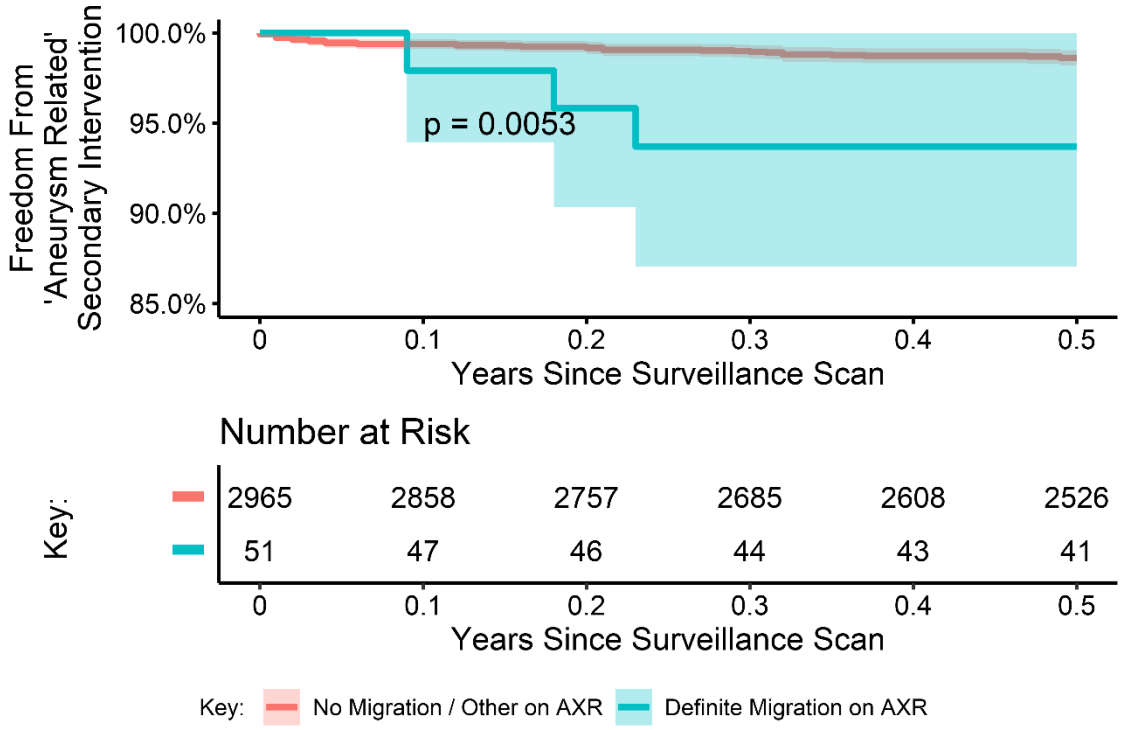
Cox proportional hazard models on, multiple imputed, data to the six months following AXR show definite migration on a AXR has a significant relationship with aneurysm related secondary intervention, hazard ratio 4.57 (95% CI 1.44 – 14.52, p=0.01).

Figure 38: Freedom from aneurysm Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Categories of Migration Detected on Most Recent AXR



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from aneurysm related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by categories of migration detected on the most recent AXR. It demonstrates a no significant increase in secondary intervention rates between all categories of migration on the most recent AXR. There is a progressive increase in secondary intervention rates demonstrated the more significant the migration detected.

Figure 39: Freedom from Aneurysm Related Secondary Intervention Following EVAR Surveillance Scan, Differentiated by Definite Migration Detected on Most Recent AXR



Kaplan-Meier plot, with log rank test p-value, demonstrating freedom from aneurysm related secondary intervention following EVAR surveillance CDUS scan. Plot is differentiated by if definite migration was detected on the most recent AXR. It demonstrates a significant increase in secondary intervention rates if definite migration was detected on the most recent AXR.

2.4.4.3 Summary of Statistical Importance of CDUS and AXR Findings

Table 16 (page 92), summarises all the investigated findings and their univariate association with flow related secondary interventions.

Table 17 (page 94) summarises all the investigated findings that had a perceived causal relationship with aneurysm related secondary interventions is displayed below.

Table 16: CDUS and AXR findings and Related Hazard Ratios to Subsequent Flow Related Secondary Intervention in the Subsequent 6 Months

Finding	Hazard Ratio (95% Confidence Interval)	Statistical Significance p Value
CDUS Findings		
Scan Diagnostic (True)	1.42 (0.74 – 2.72)	0.29
All Scans Diagnostic (True)	0.67 (0.37 – 1.22)	0.20
Limb Abnormality (True)	14.935 (8.69 – 25.70)	<0.0001
Limb Abnormality on current or Previous Scan (True)	8.71 (5.02 – 15.09)	<0.0001
AAA diameter (/mm)	1.01 (0.99 – 1.02)	0.41
AAA Growth compared to largest previous measurement (/mm)	0.81 (0.67 – 0.98)	0.03
AAA size change since last scan (/mm)	1.03 (0.94 – 1.12)	0.54
AAA size change rate since last scan (/mm/year)	1.01 (0.95 – 1.07)	0.82
AXR Findings		
Limb Abnormality (True)	4.32 (1.98 – 9.46)	0.0003
Limb Abnormality on current or Previous Scan (True)	1.80 (0.86 – 3.77)	0.13

Table 17: CDUS and AXR findings and related Hazard Ratios to subsequent Aneurysm Related secondary intervention in the subsequent 6 months

Finding	Hazard Ratio (95% Confidence Interval)	p Value
CDUS Findings		
Scan Diagnostic (True)	0.83 (0.52 – 2.79)	0.67
All Scans Diagnostic (True)	0.40 (0.19 – 0.85)	0.02
Any Endoleak (True)	8.30 (4.69 – 14.71)	<0.0001
Any Endoleak on current or Previous Scan (True)	5.38 (2.93 – 9.92)	<0.0001
Graft Related Endoeak (True)	30.49 (17.31 – 53.71)	<0.0001
Graft Related Endoeak on current or Previous Scan (True)	10.52 (6.04 – 18.32)	<0.0001
Type II Endoeak (True)	1.84 (0.97 – 3.50)	0.07
Type II Endoeak on current or Previous Scan (True)	1.68 (0.95 – 2.95)	0.08
AAA diatmeter (/mm)	1.04 (1.03 – 1.05)	<0.0001
AAA Growth compared to largest previous measurement (/mm)	1.06 (1.04 – 1.09)	<0.0001
AAA size change since last scan (/mm)	1.11 (1.07 – 1.16)	<0.0001
AAA size change rate since last scan (/mm/year)	1.06 (1.04 – 1.09)	<0.0001
AXR Findings		
Effacement (True)	7.03 (3.00 – 16.46)	<0.0001
Effacement on current or Previous Scan (True)	2.54 (1.14 – 5.64)	0.02
Structural Failure (True)	4.16 (1.51 – 11.48)	0.006
Structural Failure on current or Previous Scan (True)	1.53 (0.55 – 4.21)	0.42
Definite Migration (True)	4.57 (1.44 – 14.52)	0.01

2.4.4.4 Assessment of Confounding Between Surveillance Findings in Association to Secondary Interventions

Cox proportional hazard modelling using backwards stepwise exclusion of variables was undertaken to ascertain if the number of variables measured could be reduced without materially impacting the association with flow related secondary interventions. The initial full model which includes all variables, Table 18 (page 95), was assessed for association with flow related secondary interventions and had an AIC of 741.

Table 18 : Variable Hazard Ratios to subsequent Flow Related secondary intervention within 6 months from a Full multivariate Cox PH model

Variable	Hazard Ratio within Model (95% Confidence Interval)	p Value
CDUS Findings		
Scan Diagnostic (True)	1.22 (0.92 – 12.64)	0.07
All Scans Diagnostic (True)	0.33 (0.10 – 1.09)	0.08
Limb Abnormality (True)	17.25 (2.38 – 124.95)	0.005
Limb Abnormality on current or Previous Scan (True)	0.81 (0.11 – 6.02)	0.84
AAA diameter (/mm)	1.01 (1.00 – 1.03)	0.13
AAA Growth compared to largest previous measurement (/mm)	0.80 (0.64 – 0.99)	0.05
AAA size change since last scan (/mm)	1.10 (0.89 – 1.36)	0.38
AAA size change rate since last scan (/mm/year)	0.97 (0.85 – 1.12)	0.71
AXR Findings		
Limb Abnormality (True)	6.48 (0.78 – 53.75)	0.09
Limb Abnormality on current or Previous Scan (True)	0.37 (0.05 – 2.26)	0.37

Stepwise removal of variables from the model is shown in the analysis R code (Appendix 2, page 190), but in short:

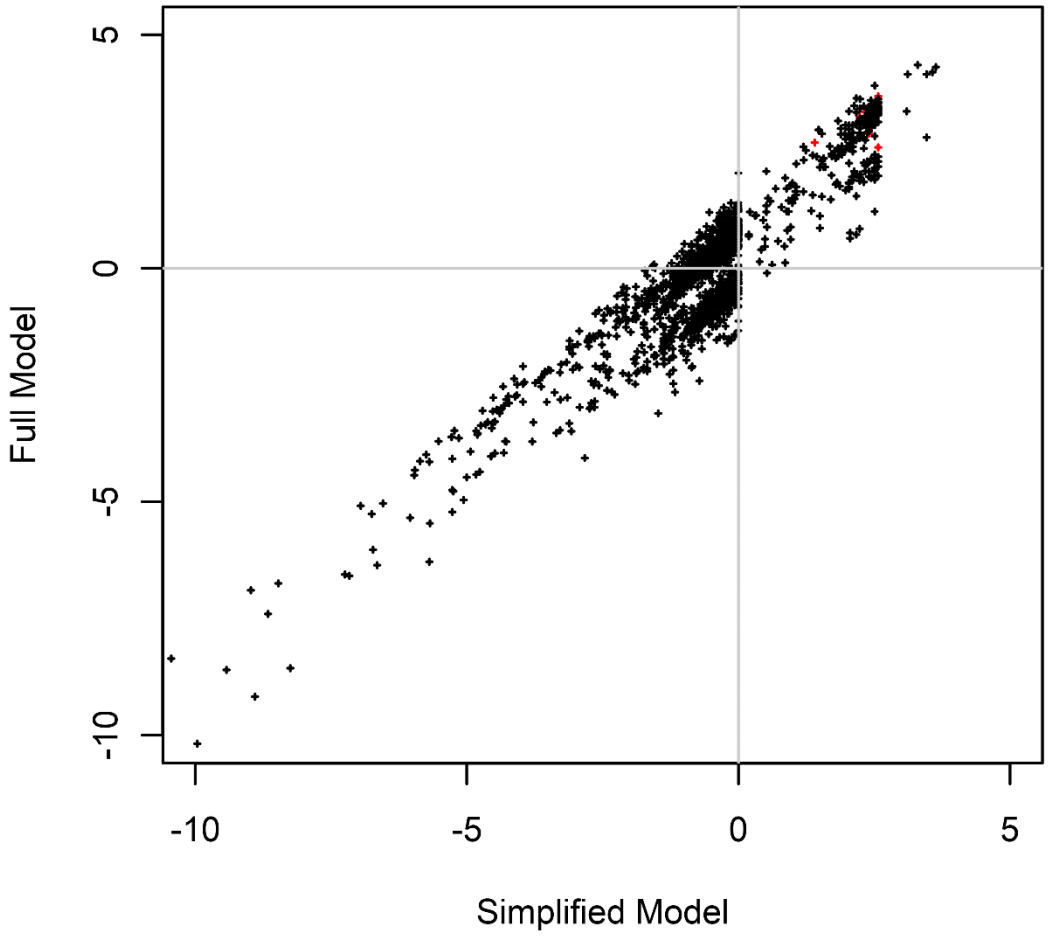
"Limb Abnormality on current or Previous Scan (True)" was removed -AIC 738,
"All Scans Diagnostic (True)" was removed -AIC 741, then
"Limb Abnormality on current or Previous AXR (True)" was removed - AIC 741, then
"Scan Diagnostic (True)" was removed -AIC 740, and finally
"AAA size (mm)" was removed -AIC 742

All further changes failed to maintain or improve AIC substantially. Table 19 (page 96), demonstrates the variables in the simplified model had an AIC of 742. Comparison of the full and simplified models numeric predictions are displayed in Figure 40, page 97. There was a very close linear relationship throughout the range of values of predictions between full and simplified model. Comparison of the models linear relationship demonstrates near perfect linearity coefficient of 0.93 (standard error 0.01). The relationship is offset by -0.51, meaning the simplified model, generally, predicts slightly lower risks but could be easily adjusted. The ROC and AUC value for both full and simplified models demonstrates both have an AUC of 0.95 and essentially identical discriminatory properties, Figure 41 (page 98).

Table 19: Variable Hazard Ratios to Subsequent Flow Related Secondary Intervention Within 6 Months From a Simplified Multivariate Cox PH Model

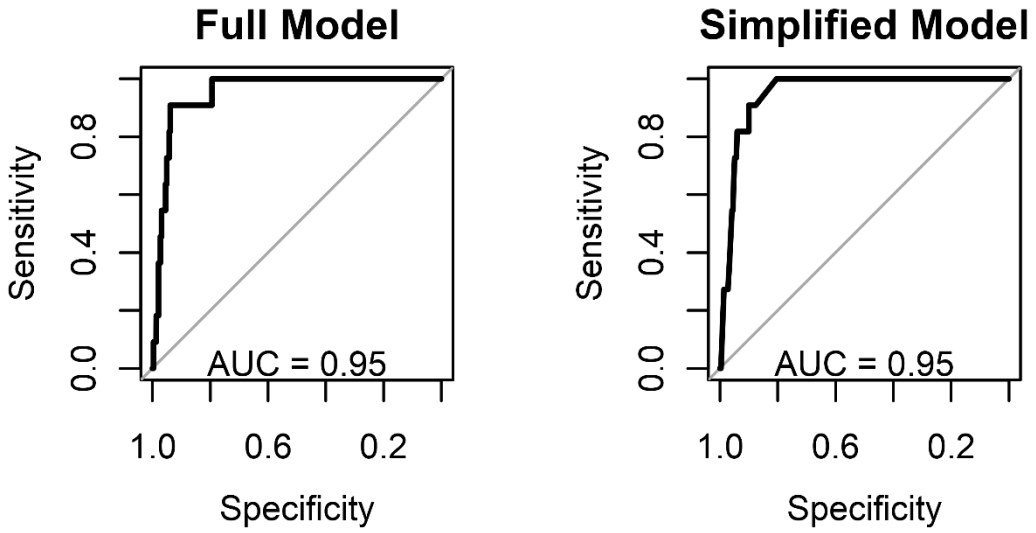
Vaiable	Hazard Ratio within Model (95% Confidence Interval)	p Value
CDUS Findings		
Limb Abnormality (True)	13.15 (7.44 – 23.25)	<0.0001
AAA Growth compared to largest previous measurement (/mm)	0.79 (0.63 – 0.99)	0.04
AAA size change since last scan (/mm)	1.07 (0.95 – 1.20)	0.25
Limb Kink on AXR (True)	2.89 (1.28 – 6.56)	0.01

Figure 40: Numeric predictions of flow related secondary interventions from a Full and Simplified Cox Proportional Hazard Model of surveillance variables



Scatter plot demonstrating the close linear relationship between the numerical values produced by two models, one using a full set of surveillance scan variables and a the other a simplified/reduced set of those variables to predict flow related secondary interventions.

Figure 41: ROC (with AUC) from a Full and Simplified Cox Proportional Hazard Model of surveillance variables to predict secondary intervention in 6 months



Receiver Operator Characteristics plots, with Area under Curve (AUC) values for two models' abilities to predict flow related secondary interventions. One model is created using a full set of surveillance scan variables and the other a simplified/reduced set of those variables. They demonstrate almost identical characteristics and AUC.

In a similar manner Cox proportional hazard modelling using backwards stepwise exclusion of variables was undertaken to see if the number of variables measured could be reduced without materially impacting the association with aneurysm related secondary interventions. The initial full model of all variables investigated for association with aneurysm related secondary interventions, Table 20 (page 99), had an AIC of 515.

Stepwise removal of variables from the full model is shown in the analysis R code (appendix x), but in short:
"Scan Diagnostic (True)" was removed -AIC 513, then
AXR "Structural Failure (True)" was remove -AIC 515, then
"AAA size (mm)" was removed – AIC 517 and finally
AXR " Definite Migration (True)" was removed – AIC 516.

All further changes failed to maintain or improve AIC. Table 21 (page 100) demonstrates the variables in the simplified model with the AIC of 516. Comparison of the full and simplified models numeric predictions are displayed in Figure 42 (page 101). This demonstrates a very close linear relationship throughout the range of values of predictions. Comparison of the models linear relationship demonstrates a very good linearity coefficient of 0.83 (standard error 0.01). The relationship is offset by-0.81,

meaning the simplified model, generally, predicts slightly lower risks. Figure 43, page 101, demonstrates the ROC and AUC value for both full and simplified models, they have an AUC of 0.92 and 0.91 respectively meaning they have almost identical discriminatory properties.

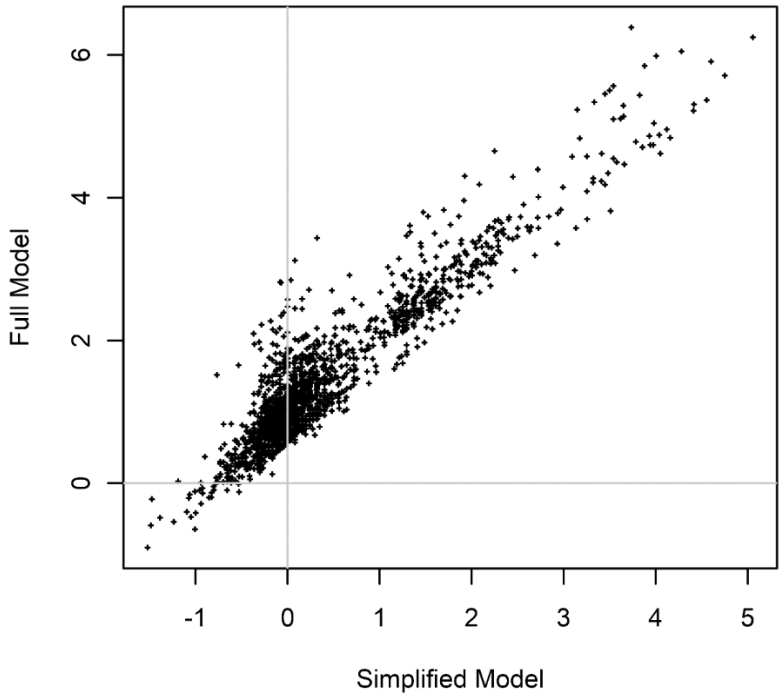
Table 20: Variable Hazard Ratios to Subsequent aneurysm Related Secondary Intervention Within 6 Months From The Full Multivariate Cox PH Model

Variable	Hazard Ratio within Model (95% Confidence Interval)	p Value
CDUS Findings		
Scan Diagnostic (True)	1.03 (0.38 – 2.81)	0.95
Any Endoleak (True)	-	-
Graft Related Endoleak (True)	19.90 (6.14 – 64.50)	<0.0001
Type II Endoleak (True)	3.22 (1.35 – 7.73)	0.01
AAA (/mm)	1.02 (0.99 - 1.05)	0.14
AAA Growth compared to largest previous measurement (/mm)	1.02 (0.92 – 1.12)	0.75
AAA size change since last scan (/mm)	1.05 (0.82 – 1.34)	0.70
AAA size change rate since last scan (/mm/year)	1.00 (0.87 – 1.13)	0.91
AXR Findings		
Effacement (True)	8.49 (3.23 – 22.31)	<0.0001
Structural Failure (True)	3.30 (1.04 – 10.48)	0.05
Definite Migration (True)	2.22 (0.59 – 8.38)	0.25

Table 21: Variable Hazard Ratios to Subsequent Aneurysm Related Secondary Intervention Within 6 Months From a Simplified Multivariate Cox PH Model

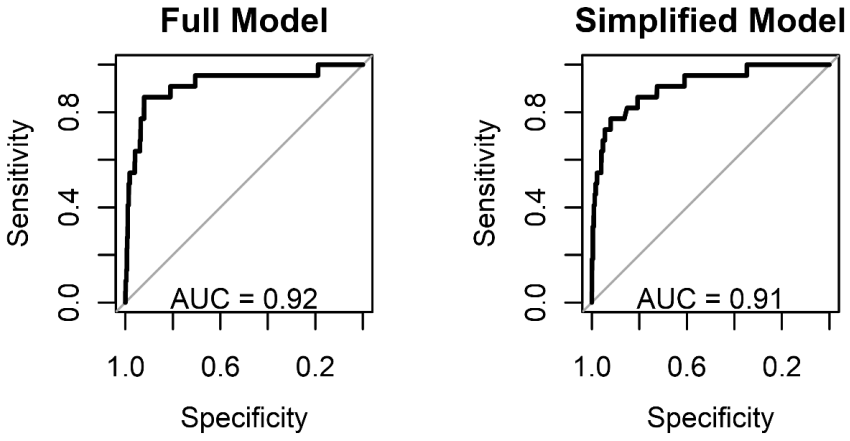
Variable	Hazard Ratio within Model (95% Confidence Interval)	p Value
CDUS Findings		
Graft Related Endoeak (True)	23.94 (8.04 – 71.28)	<0.0001
Type II Endoeak (True)	3.65 (1.61 – 8.26)	0.002
AAA Growth compared to largest previous measurement (/mm)	1.04 (0.95 – 1.14)	0.42
AAA size change since last scan (/mm)	1.04 (0.83 – 1.33)	0.71
AAA size change rate since last scan (/mm/year)	0.99 (0.88 – 1.13)	0.94
AXR Findings		
Effacement (True)	9.85 (3.82 – 25.38)	<0.0001

Figure 42: Numeric predictions of aneurysm related secondary interventions from a Full and Simplified Cox Proportional Hazard Model of surveillance variables



Scatter plot demonstrating the close linear relationship between the numerical values produced by two models, one using a full set of surveillance scan variables and a the other a simplified/reduced set of those variables to predict aneurysm related secondary interventions.

Figure 43: ROC (with AUC) from a Full and Simplified Cox Proportional Hazard Model of Surveillance Variables to Predict Aneurysm Related Secondary intervention within 6 months



Receiver Operator Characteristics plots, with Area under Curve (AUC) values for two models' abilities to predict aneurysm related secondary interventions. One model is created using a full set of surveillance scan variables and the other a simplified/reduced set of those variables. They demonstrate almost identical characteristics and AUC.

2.4.5 Predictive Model

2.4.5.1 Piecewise Exponential Model Creation

3092 CDUS scans, with related AXR findings, were used in the creation of the PEM. In total 242 of these scans were followed by secondary interventions in the available follow-up. These data were not censored at a particular time point therefore the full follow-up available was used. Follow-up had a mean duration of 2.34 years, median 1.99 (IQR 0.91 – 3.46).

The PEM timeframes were divided as described in the methods, Section 2.3.4.5.2 (page 50). That division was checked, Table 22 (page 102), to ensure a sufficient number of events occurred and patients at risk within each time frame to allow modelling and validation.

Table 22: Timeframes in Piecewise Exponential Model to Predicit Secondary Intervention following EVAR Surveillance Scan

Time Interval following EVAR (Years)	Number at Risk	Number of Events (%)
0 – 0.5	650	97 (14.9)
0.5 – 1	214	10 (4.7)
1 – 2	466	37 (7.9)
2 – 3	441	29 (6.6)
3 – 4	355	20 (5.6)
4 – 5	245	14 (5.7)
5 – 7.5	390	11 (2.8)
7.5 – 10	168	9 (5.4)
10 – 20	155	12 (7.7)

Following the described stepwise process, the following variables were selected into the model, in addition to the time intervals:

- Pre-operative AAA diameter (mm)
- AAA diameter on current CDUS scan (mm)
- Patient age at time of EVAR (years)

- Presence of any endoleak on CDUS (True / False)

2.4.5.2 Model Internal Validation

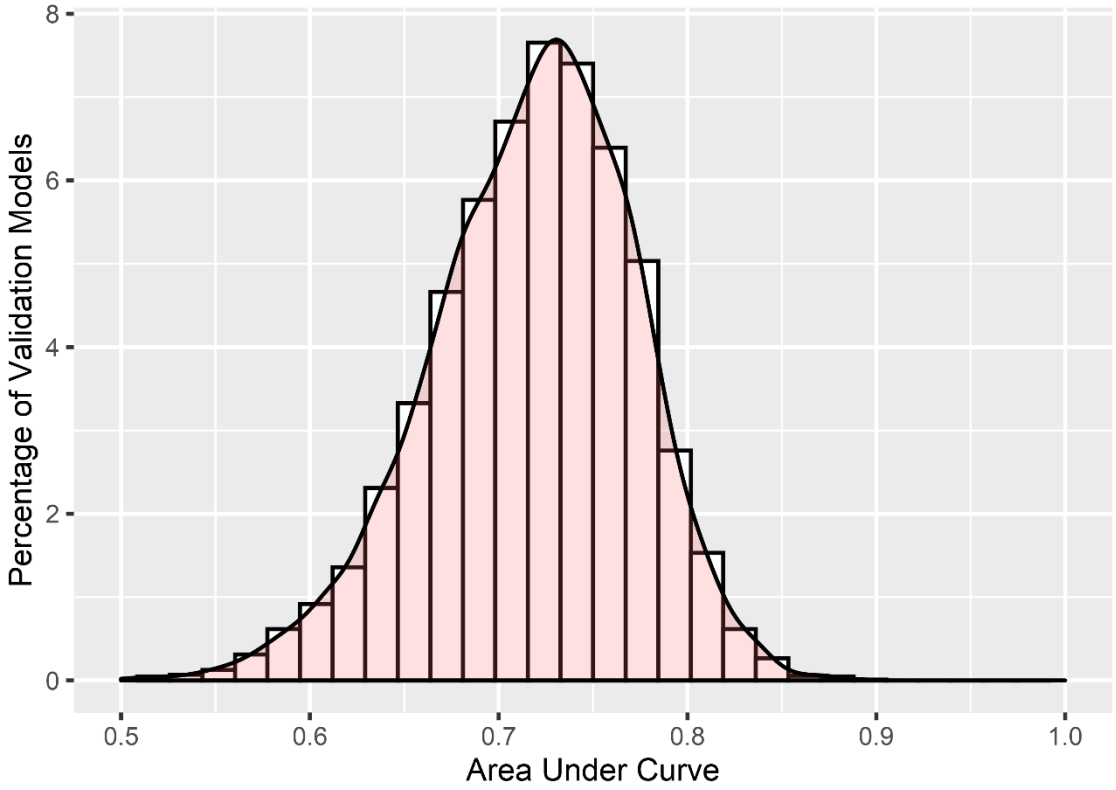
Internal bootstrapping validation as described in the methods, section 2.3.4.5.3 (page 50), returned the following coefficients for the variables in PEM.

Table 23: Variable Coefficients with produced PEM to predict secondary intervention following EVAR surveillance scan.

Variable	Estimate (Standard Error)	p Value
Time of Surveillance Scan following EVAR– Only one selected		
0 – 0.5 Years	-2.55 (0.130)	<0.0001
0.5 – 1 Years	-3.97 (0.322)	<0.0001
1 – 2 Years	-3.12 (0.178)	<0.0001
2 – 3 Years	-3.27 (0.201)	<0.0001
3 – 4 Years	-3.43 (0.237)	<0.0001
4 – 5 Years	-3.43 (0.277)	<0.0001
5 – 7.5 Years	-4.55 (0.336)	<0.0001
7.5 – 10 Years	-4.34 (0.344)	<0.0001
10 – 20 Years	-5.61 (0.307)	<0.0001
Patient / CDUS Variables		
Preoperative AAA Size (mm)	-0.03 (0.005)	<0.0001
CDUS AAA Size (mm)	0.03 (0.004)	<0.0001
Patient Age at Operation (Years)	-0.05 (0.010)	<0.0001
CDUS Any Endoleak (True)	0.69 (0.147)	<0.0001

The area under the curve (AUC) of the predictions the internal validation created had a mean and median value of 0.72, and an inter quartile range of 0.68 – 0.76 demonstrating both excellent and reproducible discrimination for this predictive model. The histogram and density curve of AUC results are displayed, Figure 44 (page 104).

Figure 44: Histogram and Density Plot of AUC Results from Internal Validation of a Predictive Model of Risk of Secondary Intervention Following EVAR Surveillance Scan



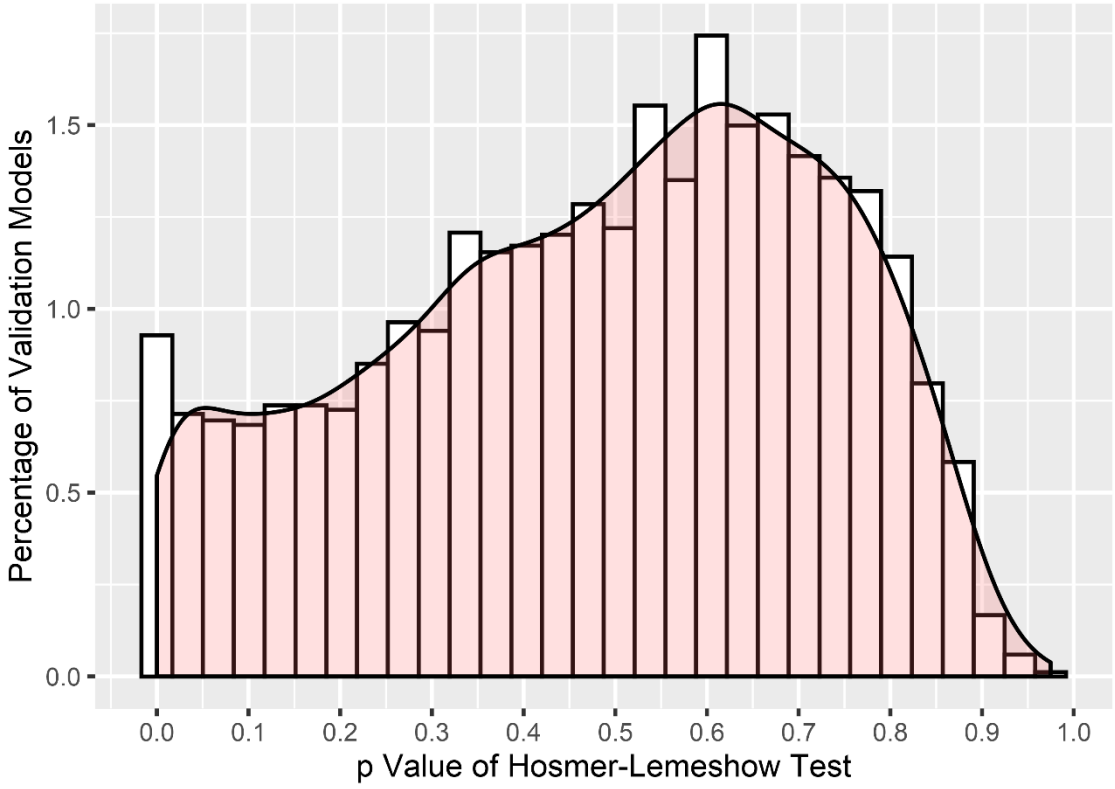
Histogram demonstrating a normal distribution of Area Under Curve (AUC) values from bootstrapping internal validation of a Piecewise Exponential Model to predict risk of secondary intervention. Distribution of the AUC values is cantered on 0.72.

Assessment of the individual bootstrap models against their 20% validation data demonstrated a median Hosmer-Lemeshow test p value of 0.51. The pattern of distribution of the p values was reviewed, Figure 45 (page 105). This shows less (~1.7%) than the permissible 5% of validation models fell within the <0.05 range. The validation models were therefore demonstrated satisfactory calibration (non-significant Hosmer-Lemeshow test) for its predictions.

The values selected for the variables in the low, mean and high risk assessment patients are displayed in Table 24 (page 106). The mean interval to next surveillance visit across the surveillance programme was 0.88 years. The cumulative risk of secondary intervention in that time following surveillance scan in these data was 4.1%.

The risk predictions of these pilot patients shows a generally linear increasing risk, with a dramatically faster incline for the ‘High risk’ patient compared to Mean and Low risk patients.

Figure 45: Histogram and distribution curve of p Value of Hosmer–Lemeshow Test in a boot strap validation of predictive score following EVAR surveillance



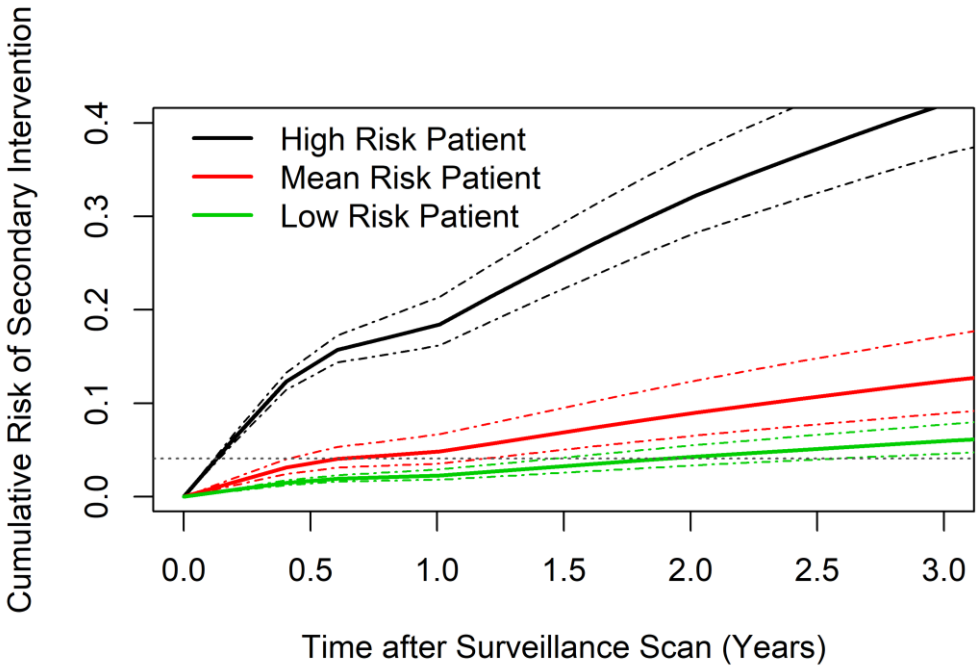
Histogram demonstrating the distribution of p values from Hosmer-Lemeshow tests of bootstrapping internal validation of a Piecewise Exponential Model to predict risk of secondary intervention. The distribution below 0.05% is below 5% demonstrating adequate calibration.

The risk predictions of these pilot patients shows a generally linear increasing risk, with a dramatically faster incline for the ‘High risk’ patient compared to Mean and Low risk patients, Figure 46 (page 106). It demonstrates the low risk patient has a gradual increase in cumulative risk, reaching 4.1% chance of requiring a secondary intervention at 2 years following their surveillance scan. In turn, the mean risk patient has a more modest incline in risk, that is not as linear, reaching a cumulative 4.1% risk at approximately 0.75 years. The high risk patient has a rapid rise in risk, that is also non-linear, reaching 4.1% before even 0.25 years have elapsed.

Table 24: Patient Variables for Low, Mean and High Risk Assessment Patients

Patient Variable	Low Risk	Mean Risk	High Risk
Time After EVAR of Surveillance Scan (Years)	4.34	3.16	0.11
Preoperative AAA Size (mm)	70	65	57
CDUS AAA Size (mm)	45	57	65
Patient Age at Operation (Years)	80	75	70
CDUS Any Endoleak	False	False	True

Figure 46: Predicted risk of secondary intervention using PEM model for Low, Mean and High Risk Assessment Patients



Future cumulative risk predictions using a Piecewise Exponential Model based on patients with low risk characteristics, mean risk characteristics and high risk characteristics. Demonstrates most of the cumulative risk is accumulated in the high risk individual.

2.5 Discussion

This observational study uses a cross-section, in time, of a complete EVAR surveillance programme to answer a number of deficits in the published literature. It is the first

substantial cohort to be examined in this manner in the field of post-operative EVAR surveillance.

It is the first study to suggest that rationalisation of EVAR surveillance can be performed on an individual basis at multiple time points throughout the post-operative period. It is also the first to address the area of which measurements and findings within each surveillance visit are likely to be pertinent to triggering a secondary intervention, the purpose of the surveillance visit.

2.5.1 Methodology

A cross sectional study (not prospective or retrospective cohorts) has several advantages over previously published studies. Regarding post-operative course of patients undergoing EVAR, the cross-sectional nature means that secondary interventions and surveillance compliance can be investigated for all time points following EVAR without having to follow a single cohort for the whole time frame, therefore offering observations that would otherwise take decades to obtain prospectively and require unrealistically large cohorts to compensate for patient attrition. These data could be collected retrospectively but this would then require looking back over a similar time frame and the problems of data loss, missing data and inaccuracies would be difficult to overcome.

Regarding surveillance scans, analysis of a cross-section of all scans performed in a surveillance programme means that these analyses naturally give appropriate weight to the volume of patients at various time points following EVAR. This particularly addresses the deficit of analysis in patients who are later in the post-operative EVAR surveillance course.

Limitations of the cross-sectional nature in this study include the inability to define what data is/was collected as would be possible in a prospective study. This places limitations on particularly multivariate analysis looking for independent associations, that might lead to causation research, as the data collected has not be collected for this purpose. It also means we were collecting information on patients with EVAR stent-grafts that are no longer available for insertion which can raise questions of applicability to future practice but equally does make it applicable to the current patients in surveillance.

2.5.1.1 Lives EVAR Surveillance Protocol and Database

This study would not have been possible without the foresight and organisational culture instigated by those clinicians within LiVES that set up the database and instilled the clinical importance of rigorous surveillance post EVAR. From the outset of the techniques use in Liverpool there were robust systems in place to ensure patients continued in surveillance until it was deemed that they were unfit for secondary intervention. The system was designed in such a manner that it was not possible for a patient to be accidently missed or forgotten and would require deliberate discharge from the surveillance programme.

The robust system underlying the protocol and database are what underpins such excellent compliance and records of the EVAR surveillance program. This is evidenced by the fact that of the 10 UK centres that participated in the EVAR-screen study,[88] Liverpool achieved the best compliance (88%) of all the centres. The clinical importance and scientific rigor placed on surveillance is also demonstrated by the critical evaluation undertaken when transitioning from CTA based surveillance to CDUS first surveillance.[78] The Liverpool – Perth protocol to standardise AXR acquisition also demonstrated the desire for standardised high quality practice.[74]

Data stipulated to be collected in the Surveillance protocol was remarkably complete and accurate within the database. Given the database's size, very few errors were discovered or corrected when corroborating the database to other primary sources of data. It is worthy of note that not a single patient who had undergone EVAR could be identified who had not been entered into the database. There was a relatively small dataset of pre-operative and peri-operative variables available within the LiVES database, this likely relates to the fact its was created close to the introduction of the technique to clinical practice and many variables now known to relate to outcomes were still to be discovered. While this data could have been retrospectively collected for contemporary patients, it was not available for historical patients who remained in surveillance several years after EVAR. The selective introduction of the available data (which would not have been corroborated for a second source) would potentially have introduced bias.

Secondary interventions were recorded into the database in an ad-hoc manner. They did not form part of the original dataset but had been added by the surveillance administrators to allow assessment of why an individual may be out of sync with the expected surveillance regimen. As such these data were significantly added to by the

process of data checking and significantly more detail obtained about those that had occurred. The data around symptoms may be particularly prone to poor quality given that it was retrieved retrospectively from what was recorded in the clinical and imaging notes. The thorough search of multiple data sources has led to a comprehensive list of those interventions performed within the service but does leave open the possibility of interventions having been performed in other centres and not reported back to LiVES. A small quantity of such interventions did occur and were recorded in clinic letters or subsequent imaging reports. Any missed secondary interventions may mean the incidence of secondary interventions is under reported or may influence the accuracy (for better or worse) of the scan findings or predictive model.

2.5.1.2 Surveillance Scans

Both CDUS and AXR were reported in a structured manner. In CDUS this was due to a standard operative procedure to their acquisition. In AXR it was due to a standard acquisition, relatively limited range of findings and the fact that the vast majority were reported by a single individual.

The breaking down of these reports to their constituent findings was undertaken in a blinded manner (blinded to patient details and outcomes) so being as unbiased as possible. As this was all performed by a single individual, the possibility of introduction of bias should be acknowledged but given the absolute nature of most findings being recorded, this system was felt to be proportional.

The level of consistency of CTA reporting was disappointing and would have required review of the core images, which was not covered by the ethical or service evaluation approvals. As such their role in this study was limited to dates of scan for compliance analysis and review of report for details of impending or previous secondary interventions.

2.5.2 Analysis

2.5.2.1 Incidence of Secondary Interventions

Incidence requires the number of events (secondary interventions) as well as the number of patients at risk to be defined. Secondary interventions were defined as detailed above. The number of patients at risk required calculation. The start point for an individual patient being at risk is unlikely to be contentious: it is either the start of the period being assessed or the time the patient started EVAR surveillance, if this was part way through

the period of data capture (because they had an EVAR or re-located to the region and joined the surveillance programme). The end point has the potential to be contentious: those patients who died, re-located away and were still in the surveillance programme at the end of the period being assessed have unambiguous end points. The small number of patients actively discharged from any further surveillance are more difficult. The majority of these were patients deemed to be physiologically unfit for a secondary intervention, we took the view that they were not at risk as they would never have had a secondary intervention, as it was felt they would not benefit from them. It could be contended that they could have had an EVAR complication that could have been treated by secondary intervention if the original EVAR had been placed in a physiologically more robust individual. This contention does not, however, reflect the reality of actual clinical practice. There were also a small number of patients who were actively discharged from EVAR surveillance before the cross sectional study period who were still alive and had no reason for discharge recorded. There was no method to corroborate that these patients were in fact discharged as they would not gain benefit.

The reporting of incidence over a 12 month period is a relatively standard measure. To make our outcomes relevant to clinical practice it then had to be stratified according to patient time after EVAR. This meant that, particularly in late follow-up, rates were more prone to fluctuations due to reduced numbers of patients at risk. This can be seen by the black lines fluctuating from zero to higher numbers, for example in Figure 13 (page 59). To compensate for this a best fit line was created that took account of the rate, which was given proportional weighting for the number of patients at risk. This best fit line was calculated using 75% of the time frame centred on the time point being calculated. Time in this calculation was log transformation, as such a high proportion of events occur in the first 6 months after EVAR. This best fit line gives a good visual approximation of true trends without the “noise” of fluctuations that result from data sparsity and analysis techniques.

2.5.2.2 Compliance

Analysis of achieved compliance has similar benefits and limitations to the secondary intervention analysis, Section 2.5.2.1 (page 109). The appropriateness of exclusion of patients actively discharged from the surveillance programme from the ‘at risk’ group is less contentious in this analysis, as patients who are not being invited for surveillance clearly cannot be compliant.

The patient characteristics association with compliance analysis was undertaken on a forward-looking (prospective) basis, as this is the perspective encountered clinically. The available patient demographics as well as time after surgery (based on the above findings) were all placed into the model. Univariate analysis was first undertaken for comparison to the literature and then multivariate analysis was undertaken to assess for co-linearity / confounding between factors. An automated backward stepwise selection was performed to look for variables that were co-linear with other variables.

2.5.2.3 Individual Surveillance Findings

2.5.2.3.1 Interval of Analysis

The association of surveillance scans and secondary interventions could be hypothesised to be the result of initial (most prevalent) surveillance scans occurring within the first month of EVAR and the high initial prevalence of secondary interventions after EVAR. As such the secondary analysis of hazard ratios once the rate of secondary interventions had settled was undertaken to ensure this was not simply co-linearity with time of scan. Visual interpretation of the point hazard curves was felt most appropriate and efficient.

2.5.2.3.2 Individual Findings Analysis

Missing data is an inevitable consequence of the methods of data collection in this study. The level of missing data in this study was low for most variables, often due to assumed negative response, with only calculated variable and size variables showing any significant level of missingness in the data set.

Assessing if data was NMAR is an important concept. There is not yet a single accepted method that is applied to this analysis in cohort studies. This was undertaken in this study by assigning missingness a variable and replacing the original variable, these were then placed into a model to predict outcome. If the missingness variable achieved statistical significance it indicated that the missing data may have been of value in predicating outcome, therefore it is potentially important and as such it was assigned the label NMAR. Multiple imputation was used in such instances.

Multiple imputations using chained equations is a relatively accepted standard method in medical research, it is used on the national UK vascular datasets.[110] The independently set methods for each variable model/calculation/imputation allows great flexibility. For logical and categorical variables, the use of Bayesian models, using all

other available data (including outcome) is the accepted standard. For continuous variables, predicative models can be individually created for each variable, however Predicative Mean Matching has been shown to be similar in outcome and is less computationally and statistically demanding. In the context of missing covariate data, Marshall et al. concluded that predictive mean matching "produced the least biased estimates and better model performance measures".[111] Kleinke similarly found that it performed well across a wide variety of scenarios, but warned it cannot address severe skewness or small samples.[112] The data in this study was not a small sample and none of the inter-quartile ranges demonstrated severe skewness.

Analysis of variables was only undertaken for association where a causative link could be hypothesised. This was to reduce the number of analyses and reduce the chance of type I error due to multiple comparisons. No adjustments were made to statistical significance levels to prevent discounting potentially important variables from further investigation.[113] This is valid in the fact that this was an investigation looking for important variables for further prospective investigation and not looking to assign causality to individual variables.

Actual analysis, within each imputation, of the data was performed using standard techniques; continuous variables were assessed using Cox proportional hazard models and categorical variables were dual analysed with Kaplan-Meier plot / log rank and Cox proportional hazard models to allow assessment of how the absolute risk developed over time as well as proportional hazard (odd ratios).

Using AXR in relation to CDUS may underplay the significance of findings on AXRs given some of the findings may be significantly older, however this method does reflect the likely clinical scenario encountered. AXR is unlikely to be used in isolation and in LiVES is normally obtained in concert with a CDUS. This is reflected by the mean, median and inter-quartile range between CDUS and AXR acquisition, section 2.4.4.2 (page 68).

2.5.2.3.3 Assessment of Confounding and Co-Linearity Between Variables by Stepwise Regression

Univariate analysis is informative when assessing association between that variable and outcome, but CDUS and AXR measure multiple variables and there will be significant interaction between these. The simplest method to assess the extent of these interactions (co-linearity and confounding) is to place them all into a predictive model (multivariate

analysis). This allows the confounding to be excluded and the true influence on the level of association (in the presence of all the other variables), to be articulated. This gives an indication of the weight that should be placed on each of these findings within the CDUS and AXR scans as currently performed.

Many of these variables in isolation or combination may in fact produce such levels of interaction as to create almost total co-linearity with other variables. As such the backwards stepwise regression modelling was undertaken to ascertain if similar levels of discrimination and predictive accuracy could be obtained with fewer variables. This would both indicate which are the dominant variables in predicting and potentially, if accuracy did not change, variables that are superfluous measurements. The remaining variables are therefore good candidates for prospective study regarding their removal from protocols to improve efficiency.

The backward stepwise process can be automated but, in this case, the interplay between variables was felt to be more important than the potential for bias and as such the process was undertaken manually. This potentially may influence the model created but also allows for the practicality of measuring variables to influence the model.

2.5.2.4 Predictive Model

The choice to use a PEM was one made based on the data in Figure 15, page 60, which shows variation in both risk of overall rate of secondary intervention at different times but also a different mix of indications for secondary intervention at differing times. Both these variables increased and decreased over time following EVAR. As such any model that did not capture the ability to vary increasing and then decreasing risk (or vice versa) over time was unlikely to ever achieve satisfactory discrimination and predictive ability for clinical use.

Model creation was unremarkable. Data missingness was sufficiently rare in the selected variables that multiple imputation was not necessary and would have been demanding for such a complex internal validation process. Internal validation was computational demanding mainly due to the number of cycles being performed, this number was selected to ensure that the true AUC and Hosmer-Lemeshow values were obtained for the model. The co-efficient values for the model from internal validation were similar to the model creation values. While minor improvements in AUC could likely have been achieved by inclusion of further variables it was felt this may then

represent overfitting to local data that would have both reduced external validity and potentially the ability to find an adequate dataset to validate the model.

Calculating the average time between surveillance visits was intended to compensate for the fact that there is a higher proportion of patient in their first year following EVAR in the surveillance programme than any other time. In that first year the patient should have undergone a scan 6 weeks following EVAR and one at 1 year post-operatively, this meant that the mean time between scans on a programme wide basis will be lower than the 1 year standard interval for the remaining time in surveillance. The only way of calculating this mean required individuals to have had a subsequent scan in the observed period of the study, this may introduce bias if there was an uneven number of individuals in the surveillance programme at the start compared to the end of the observation period. This is likely given the uneven distribution of procedures undertaken and the mentoring, both discussed in section 2.5.3.1, page 114. The calculation of the mean freedom from secondary intervention during that period gave an indication of the value to review the assessment patients on the exemplar graph.

2.5.3 Results

2.5.3.1 Demographics

The demographics section demonstrated that the patients analysed within the study, had broadly similar demographics, Table 7 (page 52), to those patients undergoing EVAR within current UK practice.[110] This adds weight to the position that these results are likely to be applicable to general UK practice.

The EVAR stent-grafts inserted into some patients, Table 8 (page 53), are earlier iterations of those still available or are still available for insertion. The 17% who had a stent-graft in ‘others’ have generally been withdrawn from the market or no longer in regular use in UK practice. This analysis was performed at patient level rather than surveillance scan level and may not represent the proportions in each of the output analyses.

The number of cases performed per a year, Figure 9 (page 53), demonstrates the gradual uptake of EVAR technology within the department between 1996 – 2004. Following the publication of the medium term outcomes of the UK EVAR trial 1,[114] part way through 2005, there is a marked increase in EVARs use consistent with those trial results. In 2009 -2013 the department undertook mentoring in the intra-operative EVAR technique

to various other local vascular departments. This accounts for the sudden increase in the number of cases as these departments' patients had their procedure within Liverpool under the mentorship of the local Liverpool surgeons. 2012 was the year of LiVES creation and merging of services and is an accurate representation of the number of annual endovascular aneurysm repairs performed subsequently. The decreased number of cases between 2012-2014 is partly accounted for by the use of the alternative Endovascular Aneurysm Sealing technique for some patients (not included in any part of this analysis). Finally the small number of cases in 2015 is the result of only part of this year being included in the analysis.

Overall survival following EVAR in LiVES is very similar to the late survival in the UK EVAR trial 1,[45] again showing applicability of these results to generality of UK practice.

The cohort of patients who had their primary EVAR within the time-frame of the data collected in the study showed a freedom from secondary intervention rate similar to the UK EVAR trial 1.[45] This has been reported to be lower in other contemporary series.[92] The numbers at risk in this analysis are heavily influenced by the mentoring patients who underwent EVAR and first post-op surveillance in LiVES but then had ongoing surveillance in another locality.

2.5.3.2 Nature of Secondary Interventions

This description of secondary indications is likely the largest detailed description of secondary interventions outside the RCTs.[40 41 45] The actual secondary interventions undertaken, Table 11 (page 57), appears uncontroversial. The proportion of secondary interventions (48%) associated with maintaining flow through the EVAR stent-graft runs contrary to the premise of current European surveillance guidance that is based purely on aneurysm related secondary interventions.[53 92] The fact that only 25% of secondary interventions occur in patients with symptoms is also markedly different from the literature. This 25% also include patients who had symptoms but failed or waited to present for clinical review.

2.5.3.3 Incidence of Secondary Interventions

Incidence of secondary intervention is not commonly reported in EVAR studies, "Freedom from [first] secondary intervention" being the preferred measure. This under recognises the total burden of secondary interventions as second and subsequent secondary interventions are rarely reported or accounted for. The actual rate (incidence)

rather than absolute number of secondary interventions is more useful in discussing risk with patients currently in EVAR surveillance rather than about to undergo EVAR.

The number of patients at risk in this analysis (particularly between 1 and 8 years) are the largest in the published literature, with the exception of the combined UK EVAR trials and national registries (registries do not offer the same data standard). The overall incidence of secondary interventions in this study of 6.1 secondary interventions per 1000 patient years, compares favourably to an analysis of stent grafts in the UK EVAR trails, which showed a rate of 7.0 and 9.4 for the two commonest stent-grafts over an median follow-up of 3.8 years.[115] Such comparisons are broad but reassuring, however note should be given to the different time frames of post EVAR follow-up featured in them. The incidence of secondary interventions following EVAR, in this study, ranges between approximately 60 and 30 interventions / 1000 patient years over the 15 years following EVAR. This rate of interventions, along with the low rate of symptoms, makes a compelling argument for the ongoing use of surveillance.

The incidence of aneurysm related secondary interventions is remarkably stable at approximately 25 interventions / 1000 patent years over the 15 years. Looking at the raw data a trend toward more significant interventions, i.e open conversions and total endovascular re-lining can be seen as time passes, however these are small numbers that would not withstand statistical analysis.

The rate of flow related secondary interventions is more variable, between approximately 10 and 50 secondary interventions / 1000 patient years, over the first 15 years following EVAR. The early predominance of secondary interventions is not surprising, but the late incidence is a novel observation not described in the literature and almost entirely accounts for the late increase in the total rate of interventions. Review of raw data does not seem to support the same pattern of complexity of interventions with open interventions appearing evenly distributed with endovascular procedures. Surveillance that detects impending flow related complications seems indicated particularly in the early and late surveillance periods.

2.5.3.4 Compliance Following EVAR

This analysis shows an exceptional high rate of compliance (>95%) till 10 years following EVAR. This high rate of compliance is almost certainly down to the systematic approach taken to achieving compliance with surveillance in the LiVES

EVAR programme. Compliance from 10 – 15 years following EVAR reduces to nearly 50%, with relatively few individuals at risk during this period.

This analysis confirms that excellent compliance is achievable through till 10 years following EVAR. The system in use in LiVES demonstrated the best compliance in EVAR-screen,[88] and may offer a model for other centres in achieving compliance.

The sudden deterioration in compliance from 10 years onwards does however indicate there is some other factor that influences compliance, this factor must be patient centred - as the same systematic approach to achieve compliance is used consistently through-out follow-up. It may also indicate that measuring compliance just at the end of a study period may not give an accurate reflection of compliance throughout the period and may explain the differences between surveillance efficacy studies.[70 71 88] This observation would make de Mestral et al. study, which uses a measure of compliance over the totality of follow-up, the most appropriate approach in the published literature. Their study demonstrated that the larger the proportion of time compliant with follow-up was associated with a lower risk of death.[71]

2.5.3.5 Patient Characteristics Associated with Future Compliance

Univariate (unadjusted) analysis, Table 14 (page 65) of these factors broadly concur with the literature suggesting: older patients, patients who are further into their surveillance and patients who had operations in earlier years are all less likely to be compliant with their next surveillance visit. Differing from the literature, increasing distance to surveillance centre (km) was associated with, a small, increase in compliance. This may indicate the short distance to surveillance experienced in this study is within the acceptable travel distance for patients. It may also indicate the small number of tertiary patients travelling very large distances have much higher compliance than local patients travelling short distances. There were insufficient numbers of tertiary referral patients to be able to investigate this further. Gender notably showed no association with compliance, which is surprising given the literature on the subject that suggest males are less compliant with most healthcare interventions. All of these associations were small on an individual factor basis. Adjusted analysis demonstrated the calendar year of operation and time after EVAR were dominant factors in compliance with advancing years being associated with decreasing compliance for both.

Stepwise regression is a gross technique to reduce the number of variables so reducing co-linearity, but it is clinically indiscriminate in factors excluded. The simplified model,

Table 15 (page 65), maintained the same overall predictive ability therefore making it suggestive that gender and pre-operative AAA size are unlikely to have any significant association with compliance. Within the model, the dominance of 'year of EVAR' and 'time since EVAR', with only a small effect of absolute age, suggest that patient attitude / understanding and attrition to tolerance of surveillance are potentially the most important factors to study in improving patient compliance. This hypothesis is theoretically supported by the improved association of compliance in those who have previously had a secondary intervention, thus having benefitted from surveillance and likely increased understanding of the importance of surveillance.

All of these findings have to be taken in the context of the underlying system used to manage surveillance in LiVES. In particular the active discharge of patients physiologically unfit for secondary interventions that may still be invited, decline and therefore classed as non-compliant in alternative systems. This may account for this study finding a relative low significance of absolute age.

Association is not causation. It is however an appropriate method of trying to define targets for causation research or targets for future studies to trial interventions to improve compliance.

2.5.3.6 Surveillance Scan Findings: Interval of Effect

The analysis of point hazard ratio for undergoing secondary intervention following surveillance scan, Figure 18 (page 67), demonstrates compelling evidence that secondary interventions are associated with surveillance scans. The replication of the curve shape, Figure 19 (page 67), at a lower ratio in scans that occurred after the initial post-operative period demonstrates that this is unlikely a cofounding effect of both events occurring in high proportions in early (<0.75 years) EVAR follow-up. 0.5 years is visually an appropriate time to select for review of causative effect given the shape of both of these curves, both had reached a stable base line risk by this time point.

2.5.3.7 Surveillance Scan Findings: Correlation with Secondary Interventions

Univariate analysis of the binary diagnostic/non-diagnostic variable on current CDUS scan showed no association with aneurysm or flow related secondary intervention. Analysis of the cumulative diagnostic/non-diagnostic on any CDUS scan similarly had no association with flow related secondary intervention. Aneurysm related secondary interventions however did show an association with such a cumulative finding of all

CDUS being diagnostic. This is logical if the undiagnostic finding is given more in scans of poor quality imaging, thus inhibiting the triggering of secondary interventions. The different but relatively consistent gradients in the Kaplan-Meier plot, Figure 23 (page 72), are suggestive of an underlying difference in risk of triggering a secondary intervention. This is potentially suggestive that patients with an undiagnostic CDUS are not having alternative imaging as likely to trigger secondary intervention as those who have diagnostic CDUS or alternatively it is a cofounding factor for patients less suitable or in need of secondary intervention.

The findings of the univariate analysis of: any, graft related and Type II endoleaks can be discussed in concert, a finding of any endoleak was common (18% of scans) and graft related endoleaks rare (2% of scans) both are statistically associated with aneurysm related secondary intervention following CDUS scan. Type II endoleaks (15% of scans) were not statistically associated with secondary intervention ($p=0.06$), consistent with practice supported by publications suggesting that isolated type II endoleaks are not associated with increased rupture risk.[54] The odds ratio, of secondary intervention, following graft related endoleak diagnosis on CDUS is very large but does not fully articulate that only approximately 30% of patients underwent intervention in the 6 months following CDUS. The intervention rate in all endoleaks is not totally accounted for by those which were classed as graft related and the presence of any endoleak has an ability to account for miss classification of type II endoleaks that were deemed to require intervention.

The cumulative finding of all three endoleaks findings appeared to simply reduce the effect on odds ratios in all the classifications. It had been hypothesised that Type II endoleaks on a previous CDUS might increase secondary interventions following subsequent CDUS if growth was demonstrated. This was not seen in the 6 months following subsequent CDUSs analysed. As such the strongest associations in endoleak diagnosis on CDUS, in terms of triggering secondary intervention, are classification as a graft-related endoleak on current scan and presence of any endoleak on current scan.

Finding a limb abnormality on CDUS was a common (12% of all CDUSs) finding and was associated with flow related secondary intervention in approximately 10% of cases by 6 months. The hazard ratio (14.9) and statistical significance ($p<0.0001$) suggest this is a highly effective measurement in terms of association with secondary interventions. It is, from this data, not possible to fully understand the threshold for reporting a limb abnormality, this would require further prospective evaluation. Similar to endoleak

diagnosis the cumulative finding diminished the association but not statistical significance of the finding. This suggests that most interventions are associated to de-novo limb abnormalities being detected rather than progression of previously known abnormalities.

Absolute AAA size was notably smaller on surveillance CDUS than the pre-op size (Median 56 vs 62mm) with scans having a median time after EVAR of 2.8 Years. This suggests, on a programme wide basis, that aneurysm regression after EVAR is likely approximately 2.1 mm/ year. This is very similar to linear models for expansion,[19] discussed in section 1.1.2 (page 3). Flow related secondary interventions had been hypothesised to be associated with an aneurysm size due to associated tortuosity. No association could be established, $p=0.41$. Aneurysm related secondary interventions were statistically associated with absolute size ($p<0.0001$), but with a very low hazard ratio 1.04 per 1mm size increase. Meaning only very large sized aneurysms were likely to trigger such interventions. This fitted with clinical practice where far more emphasis is placed on size changes rather than absolute size.

Maximum AAA growth was the calculated variable to assess for size increases. Given the data set it was not possible to assess for total shrinkage as largest previous size was not recorded in the same manner as smallest. If the current scan was smaller than maximum size then this was recorded as 0mm. This had an unexpected association with flow related secondary interventions, making them less (rather than more) likely – hazard ratio 0.81 per 1mm size increase. This association is clinically significant enough to warrant consideration. It should be noted that inability to measure negative sizes may have introduced a measurement/analysis error that created this finding. Surprisingly, there was a lesser association to aneurysm related secondary intervention – hazard ratio 1.06 per 1mm size increase.

Recent AAA Growth (size change) had no significant association with flow related secondary intervention and was able to measure reducing aneurysm size. It did however have a strong association (statistically and clinically) with aneurysm related secondary interventions. For each 1mm size increase hazard ratio was 1.11. This measure does not take account of the time frame this occurred over, that time frame between surveillance was felt clinically appropriate by the treating team. As such it may be a useful marker in any surveillance programme that uses differing surveillance intervals for individual patients.

Recent AAA growth rate uses the above information in addition to the time interval between scans. Once again that there was no association with flow related secondary intervention. It did have an association with aneurysm related secondary intervention, however this was less clinically important with a hazard ratio of 1.06 per 1mm/year size increase. This was likely due to the distribution of this finding being the same as recent AAA growth rate, potentially due to the annual surveillance programme meaning most scans were 12 months apart.

Size measures in their totality appear to demonstrate that AAA size change since last scan and compared to smallest size have a stronger association with triggering secondary intervention than rate of that size change or the absolute AAA size. This would be a logical extension of a clinical practice in which there is a threshold of size change that clinicians will tolerate and above that trigger's further investigation with a view to intervention.

Effacement demonstrated on AXR is an unusual finding with only 7% of CDUS scans having a corresponding AXR that detected effacement. The hazard ratio, 7.03, is a reflection of the low number of patients with effacement who went on to have intervention (approximately 10%) in the six months following its discovery. This reflects that intervention for signs of a failing proximal landing zone are often complex, and frequently require extension into the visceral segment of the aorta. This complexity is likely reflected in the Kaplan-Meier plot, Figure 32 (page 84), showing that secondary interventions do not diverge till after 0.1 year (~ 6weeks). This delay reflects time being taken to further investigate, plan and acquire stent-grafts to allow secondary interventions to take place. Similar to CDUS findings cumulative finding of AXR effacement demonstrate a lesser association, hazard ratio 2.54, than currently detected effacement.

A structural failure on AXR (excluding a single barb fracture) was a rare finding with only 2% demonstrating such a failure. The hazard ratio, 4.16, for secondary intervention was low considering the finding represents a physical breakage of the metallic stent-graft structure. This is likely influenced by its rarity and uncertainty regarding its importance to durability. As with effacement a cumulative finding diminished the association to the point of not achieving statistical significance, p=0.42.

Limb abnormality on AXR was again a rare finding with only 3% of CDUS scans associated with an AXR which demonstrated it. It was strongly statistically associated

with flow related secondary interventions, p=0.0003. The hazard ratio, 4.32, indicates strong clinical significance. A cumulative finding of limb abnormality again reduced association to the point of no longer being statistically significant.

Migration on AXR was separated into groups in reports. Of these only ‘definite migration’ had a secondary intervention rate different to the other groups. A trend appears to be present that minor migration has a, not statistically significant, increased rate of secondary intervention compared to no finding of migration, but lesser effect than definite migration. This indicates that migration may be progressive and that higher granularity to movements would allow better diagnosis of requirement for intervention. The fact that small caudal movement labelled as barb engagement are not associated with secondary intervention would suggest that it is appropriately being segregated from other types of migration or may not be a significant finding.

When all other groups were combined, a True/False finding for ‘definite migration’ on AXR it demonstrated significant differentiation between groups confirming its independent clinical utility.

2.5.3.8 Assessment of Confounding and Co-Linearity Between Variables by Stepwise Regression

The full multivariate model, Table 18 (page 95) relating to flow related secondary interventions shows the over whelming dominance of a current CDUS limb abnormality with a hazard ratio of 17.25. A limb abnormality on AXR show the second largest influence with a hazard ratio of 6.48, all the remaining variables show very minor effects. Aneurysm size variables are interesting in that the absolute aneurysm size has virtually no association with flow related secondary intervention will total size increase actually appears to have a protective effect and conversely shrinkage increases the risk. This can be explained by growing aneurysm changing morphology being more likely to pull limbs out from their seal zones leading to aneurysm related (not flow related) secondary interventions. Shrinking aneurysms are more likely to compress stent-grafts into a smaller space that can lead to limb kinking and the need for flow related secondary interventions. As such kinks are likely to be present or absent rather than degrees of kinking the absolute change in size rather that the rate of size change is the logical measure to discern this. Rate of change would be more likely to influence chance of future secondary intervention.

The stepwise regression bears out many of the above points with all but size variables, CDUS limb abnormality and AXR limb abnormality being excluded quite readily. The non-exclusion of AXR limb abnormality could be contested as it led to a 3 point rise in the AIC, however in the context of a modality that was required for aneurysm related secondary interventions its inclusion was felt appropriate. This meant that CDUS limb abnormality (with its non-specific nature), absolute size increase, most recent size change and AXR limb kink produced the simplified model, Table 19 (page 96). In practice this represent examining the limbs and taking an aneurysm measurement on CDUS and an AXR on each surveillance visit in the context of assessing for need of flow related secondary intervention.

The full multivariate model, Table 18 (page 95) relating to aneurysm related secondary interventions shows a similar single variable predominance in the form of the presence of a graft related endoleak, hazard ratio 19.9. Presence of a type II endoleak, AXR effacement, AXR structural failure and AXR definite migration all have moderate influence but again size variables individually have surprisingly little influence.

Stepwise regression again excluded absolute aneurysm size as well as structural failure on AXR – likely due to its rarity. The exclusion of AXR definite migration was surprising and may simply represent co-linearity with effacement. In reality migration is likely to easier to define on AXR than effacement as they may represent 10x larger size changes/movements on AXR for migration of effacement. The ongoing inclusion of change and rate of change in aneurysm size but exclusion of absolute sizes is probably the result of the complex anatomical changes that occur during size changes. The likely cause of most of this is the differing baseline size of patients undergoing EVAR but also the altering course of aneurysm sizes over time reflecting alterations in patient risk and the result of having already developed a complication.
These complexities are unlikely to ever be adequately dealt with in a proportional hazard model and are well suited to linear discrimination analysis as has been proposed in sac rupture risk.[36] The cross-sectional nature of this study means that we do not have serial size measurements for all patients from implant to current CDUS to allow this to be undertaken.

In summary a CDUS looking for endoleak (absent/ graft related/ type II), aneurysm size (in comparison to previous measurements), limb abnormality (absent/ present) and AXR to assess for effacement (and possibly migration) within a model demonstrate the same predictive power as all the 10s of variables currently collected. A prospective study

looking at a simplified surveillance CDUS/AXR protocol would appear warranted. Similarly attempts to improve the granularity of migration diagnosis and effacement detection on AXR are likely to be beneficial. Finally, a tighter definition of presence / absence of limb abnormality on CDUS would potentially improve intra-operator reliability.

2.5.3.9 Predictive Model

PEM was created and internally validated, the resultant variable coefficients are interesting (Table 23, page 103) in that the initial main influence is from time after EVAR (Years). All time coefficients reduce likelihood of intervention from the high risks produced by the patient and CDUS variables. This is seen most significantly in the 10-20year time frame where the reducing power of the time variable is more than twice that of 0-0.5years. This could be for two reasons one the CDUS variables become more extreme in this late stage follow-up and the other is that there is indeed a higher threshold for intervention (due to patient age and potentially failed previous interventions). This runs country to the secondary intervention prevalence element of the study which is more robust method of examining this area. Presence or absence of any endoleak on the CDUS and current CDUS AAA size (per mm) being the next most influential, dependent on how large the AAA is. In a large AAA, CDUS size could be the most influential variable of all. Finally the fixed variable of patient age at operation and pre-op AAA size both reduce the likelihood of intervention the larger they are. It is interestingly the CDUS and pre-op AAA size are exactly matched coefficients. If an aneurysm is larger than pre-op then there is an increased likelihood of intervention and vice versa, when they are equal they have no influence on the model. This is of course logical in that shrinking aneurysm sizes are an indication of current treatment success. Although reducing aneurysms may be associated with increased flow related secondary intervention the reduction in aneurysm related secondary interventions mean the overall risk of secondary intervention is reduced.

An AUC of 0.72 is a good improvement on a surveillance programme that has no patient specific elements (e.g. everyone comes back at the same interval regardless of findings or time since operation). If that was the case and you fully implemented a risk model to define the interval to next surveillance that was based on not changing the mean risk of secondary intervention you would see an up to 44% increase in programme efficiency. In reality this is difficult to calculate as some patients are brought back for increased intervals of surveillance in the current programme and to fully realise the

possible increased efficiency some patients would be placed on uncomfortably long surveillance intervals that clinicians and patients are unlikely to be willing to accept. As such any implementation would have to have "collars" of minimal intervals to next surveillance – to allow changing findings to occur and maximum intervals to surveillance to account for the increasing confidence intervals and uncertainty around predictions that are further from scans.

The tight IQR (0.68 – 0.76) of the AUC values and narrow distribution on the histogram (Figure 44, page 104), on internal validation demonstrate the stability and reliability of the PEM in this cohort. The fact that none of internal validation models had a AUC greater than 0.9 suggests that there are some secondary interventions that these set of data are simply not able to predict. The 13% of secondary interventions performed as an emergency would seems a remarkably similar number and might warrant further investigation.

Figure 45 (page 105) shows a skewed distribution across the spectrum of p values from the Hosmer-Lemeshow test. It concentrates around $p \approx 0.6$ with less than the permissible 2.5% falling below 0.05 demonstrating satisfactory calibration.

The assessment patients allow the potential practical use of the PEM to be demonstrated. The patients represent Low/Mean/High risk variables into the model not a low risk output from the model. This is important to differentiate as it is unlikely the mean risk output from the model would suggest a 0.6year surveillance interval. These hypothetical patients do however clearly delineate the huge difference in individual patients risks over time and the potential folly of trying to treat them all the same as far as surveillance interval is concerned.

2.6 Summary

The findings of this study demonstrate the indication for secondary interventions to be split between maintaining aneurysm treatment efficacy and maintain flow to the lower extremities. This runs contrary to the focus of the majority of the current literature which often does not consider flow related secondary interventions. The secondary interventions include treatments for limb occlusion, acute limb ischemia and even lower limb amputation all of which demonstrate the importance of this area of surveillance. This study shows the global incidence of secondary interventions to be generally consistent, throughout the majority of the post-operative period, up to 15 years following EVAR. There is however a high initial and increasing late (10-15 years)

incidence of interventions. These are exclusively associated with increased rates of flow related interventions while aneurysm related interventions are grossly static. This may run counter to assumptions that with increased treatment failures in late follow-up, seen in the UK EVAR 1 trial, there may be an increased aneurysm related secondary intervention rate. This assumption was not demonstrated in this study.

It has demonstrated that compliance with surveillance following EVAR can be maintained at very high levels for a prolonged period when the use of a systematic approach with safeguards in place is employed. There, however, does ultimately appear to be a limit to the time in or amount of surveillance patients will tolerate and in more recent years (as EVAR has become the most common treatment) this may be lowering.

This study demonstrated that there is an increased rate of secondary interventions up to 6 months following surveillance scan, this is a strong suggestion of causative effect of surveillance on triggering secondary interventions that is disputed in the literature. It demonstrates the large amount of confounding and co-linearity that exists between variables measured on CDUS and AXR in their association to secondary interventions. These scanning protocols should be rationalized and prospectively studied, so improving the efficiency with which these scans are undertaken.

Finally, this study has demonstrated that it is possible to predict their future risk of secondary intervention based on their current surveillance findings, at any point in their post-op surveillance. This has been validated internally and shown to have good accuracy and discrimination between risk. This risk prediction can be used to adjust the interval to next surveillance scan so increasing the efficiency of the surveillance protocol and the efficiency (and therefore cost effectiveness) of post EVAR surveillance programs.

3 Prospective Study Comparing Contrast Enhanced Ultrasound To Time-Resolved Computer Tomography Angiography

Detection and correct characterisation are required for a complete diagnosis of any endoleak, such a diagnosis is an imperative feature of surveillance imaging in preventing failures of endovascular aneurysm repairs (EVARs). The gold standard for diagnosis of endoleaks is catheter directed digital subtraction angiography (DSA), which is not a practicable choice for surveillance. Computer Tomography Angiography (CTA) is the historical surveillance modality of choice but concerns over cost, potential nephrotoxicity of contrast agents and repeated radiation exposure led to Colour Duplex Ultrasound Scan (CDUS) becoming an established alternative. CDUS has a lower sensitivity and specificity for diagnosing endoleaks compared to CTA. Contrast Enhanced Ultrasound Scan (CEUS) represents an improvement of ultrasound imaging technology but comparisons against CTA report widely varying results, likely due to technical factors of CEUS and limitations of single-phase CTA.

The development of time-resolved CTA (tCTA) offers timing information that more closely mirrors the dynamic information available from DSA. Theoretically CEUS and tCTA have the best potential for diagnostic accuracy, without using invasive catheter angiography. The aim of this study was to 1) compare diagnostic values of CEUS and tCTA and 2) investigate the utility of other measurements available from tCTA and CEUS.

3.1 Background

EVAR is associated with complications which sometimes require secondary interventions to maintain the treatments efficacy. This has been recognised since the inception of the technique and confirmed by the secondary failure rate in observational studies as well as randomised controlled trials (RCT).[40-43] Therefore periodic surveillance imaging is recommended for life following EVAR.[17 68] The importance of post-EVAR surveillance remains enduring, its value further highlighted by the analysis of 15-year follow-up after EVAR in the landmark RCT,[45] which showed late aneurysm related mortalities in the EVAR arm suggestive of treatment failure.

The commonest complication in EVAR surveillance is an endoleak.[47] Endoleaks are classified based on the source of blood flow,[48] but can be grouped into stent-graft related (types I and III) and type II (non stent-graft related) endoleaks. Stent-graft related endoleaks generally transmit high pressure causing a high risk of aneurysm expansion/rupture (treatment failure)[49 52]. In contrast, type II endoleaks generally run a benign course, particularly in the absence of aneurysm expansion.[52] With regards to endoleak imaging, accurate detection and characterisation improve diagnostic utility of surveillance, in particular with an emphasis on distinguishing stent-graft related endoleaks from type II endoleaks. Digital subtraction angiography (DSA) in multiple planes and a high frame rate of acquisition is the diagnostic gold standard of endoleak imaging. High frame rates are required to demonstrate endoleak haemodynamics (inflow and outflow) for accurate characterisation. DSA is not tenable to be used as surveillance imaging due to its invasive nature, high cost and relatively high radiation exposure to the patient.

Historically EVAR surveillance was undertaken using Computer Tomography Angiography (CTA). A single arterial phase CTA was the most frequently used modality, although selectively or routine additional phases can be added such as unenhanced, venous, and even delayed phases. Concerns over cost, use of potentially nephrotoxic contrast agent and repeated radiation exposure led to alternative imaging modalities being investigated and implemented in surveillance regimens. Colour Duplex Ultrasound Scan (CDUS) is the most widely used imaging modality in the UK, currently.[87] CDUS is reported to have a lower sensitivity and specificity to detect stent-graft related endoleaks compared to CTA. [73]

Contrast Enhanced Ultrasound Scan (CEUS) has been investigated as an adjunct to CDUS in the hope of improving sensitivity to endoleak detection. CEUS involves intravenous injection of a microbubble contrast which remains in the blood, allowing improved detection of endoleaks, section 1.3.7 (page 21). CEUS also allows continuous (dynamic) or real time monitoring of the aneurysm and endoleak as the contrast agent arrives in the endoleak. Modern microbubble agents are eliminated by the respiratory system, thus avoiding nephrotoxicity. A recent review of 30,222 administrations of a CEUS contrast agent demonstrated a low adverse reaction rate of 0.020%.[81] CEUS also obviates the radiation exposure associated with CTA.

Time-resolved CTA (tCTA) was first described for endoleak detection in 2010.[116] The single arterial phase is replaced by multiple phases in tCTA, which are typically of lower radiation dose. This allows the contrast to be observed as it passes into, through and out of the stent-graft and any endoleak present. tCTA therefore offers dynamic observations of endoleaks, such as flow direction and filling speed, while still retaining many of the advantages of CTA (3D multi-planar reconstruction etc.) which closely mirror the advantages of multi-planar DSA. A large enough number of measurements regarding endoleaks on tCTA[117] are available to allow the technique to be refined. This means a standard arterial phase in CTA can be replaced with a tCTA that is aimed at detecting stent-graft related endoleaks, without increasing average radiation exposure for the patient. Given that the timings and interpretation of tCTA are sufficiently understood it is timely to do a comparison of CEUS to the improved comparator of tCTA. This is an improvement on the limitations of previous studies as it compares CEUS to a (semi) dynamic form of CTA imaging as an improved comparator standard.

3.2 Aims

We aimed to show the sensitivity and specificity of CEUS to detect graft related and other endoleaks, in comparison to the improved reference standard of tCTA. These data collected may help develop a more efficient protocol for CEUS and a new role in guiding the timing of phases in CTA.

3.3 Methods

The protocol for this research was submitted for publication before recruitment was completed and before any analysis was undertaken.[118]

3.3.1 Study Design

This was a prospective single centre comparative study of paired diagnostic imaging modalities, designed to comply with the "Standards for Reporting Diagnostic accuracy studies" (STARD).[119 120] Participants were recruited from Liverpool Vascular and Endovascular Service (LiVES), a city-wide vascular service in the UK. LiVES is arranged in a "hub and spoke" configuration locally and regularly accepts tertiary referrals for complications of previous aortic surgery at other centres. Routine EVAR surveillance is predominately undertaken using CDUS and abdominal radiograph (AXR).[78]

3.3.2 Recruitment

We recruited participants who potentially had a type I/III endoleak present, as this was the finding for the primary outcome of this study. To reduce the ethical apprehension regarding radiation exposure involved in the study we elected to recruit patients who were due to undergo dual phase CTA and CEUS in their standard care. Within the host institution these investigations are used to further investigate patients with aneurysm growth following EVAR, suspected graft related endoleaks or endoleaks of unknown characterisation.

Focusing the study in this manner, we reduced the number of participants and so the total number of patients, that we change investigations away from standard practice. The above changes were felt to be sufficiently large enough away from standard care it was also considered imperative that participants gave personal informed consent, meaning those not able to consent where excluded. This established the Inclusion Criteria, Table 25 (page 130).

Table 25: Inclusion criteria for prospective study comparing CEUS to tCTA for endoleak detection and characterisation

Inclusion Criteria
Aged 18 or over
Able to give informed consent
Undergone an infra-renal EVAR of abdominal aortic aneurysm
Planned for CTA and CEUS of EVAR

There were two identified streams of recruitment;

1. Immediately following EVAR when the operating surgeon felt that the participant had a type I/III endoleak on completion angiography. These participants are more at risk of having a type I/III endoleak on their routine initial post-operative CTA as it is already suspected.

2. Participants who have had aneurysm expansion or type I/III endoleak suspected on standard surveillance (CDUS) who are planned for a CTA and CEUS.

Patients were identified by staff involved in their clinical care and then referred to the study if the patient was interested in being considered for participation. This prevented the screening of identifiable patient details by study investigators.

Once patients had been referred to the study investigators establish contact in person or by phone. Exclusion criteria were checked and the consent process commenced. Exclusion criteria, Table 26 (Page 131), were established by factors/characteristics that would prevent participation or make obtained imaging un-diagnostic.

Table 26: Exclusion criteria for prospective study comparing CEUS to tCTA for endoleak detection and characterisation

Exclusion Criteria
Unable to receive CTA Contrast
Iodine contrast Allergy,
Insufficient renal function for standard outpatient contrast study (eGFR <45)
Hyperthyroidism
Unable to receive CEUS contrast
Previous reaction to Sonovue® (Ultrasound Contrast)
Allergy to sulphur hexafluoride (used in electrical industry in circuit breakers, switch gears and electrical equipment)
Recent acute coronary syndrome or unstable angina, typical angina at rest or frequent or repeated angina/chest pain – all within previous 7 days
Recent coronary intervention
Previous embolization of artery in region of EVAR (affects imaging quality)
BMI >30 (affects imaging quality)

3.3.2.1 Recruitment Prediction

Based on recent years data, section 2.3.2 (page 34), LiVES performs 590 CDUS scans/year, for infrarenal EVAR surveillance, Table 27(page 132). Previous analysis (Section 2.3.4.4, page 45) of a sample of 1592 of the above scans has shown an incidence of 2.3% of Type I/III endoleaks and 6.1% of unexplained aneurysm expansion >5mm of 6.1%. Giving a potential 49.6 (8.4% of 590) participants from CDUS surveillance. In addition to a small (unpredictable) number of participants who were referred following EVAR with Type I/III endoleaks on completion angiogram, we had estimated 2 / year.

We anticipated 20% of participants would be excluded (predominately due to BMI>30) or decline to participate. We therefore based our recruitment predictions on 41 participants recruited / year. This gave a predicted time to recruit 74 patients, section 3.3.7.1 (page 137), of 22 months.

Table 27: CDUS surveillance scans in LiVES in patient who have previously undergone infra-renal EVAR, numbers by year

Year	Number of CDUS scan for Infra renal EVAR Surveillance
Apr08-Mar09	422
Apr09-Mar10	564
Apr10-Mar11	478
Apr11-Mar12	1056
Apr12-Mar13	525
Apr13-Mar14	574
Apr14-Mar15	514

Average CDUS Scans / Year = 590

3.3.3 Consent Process and Participant Journey

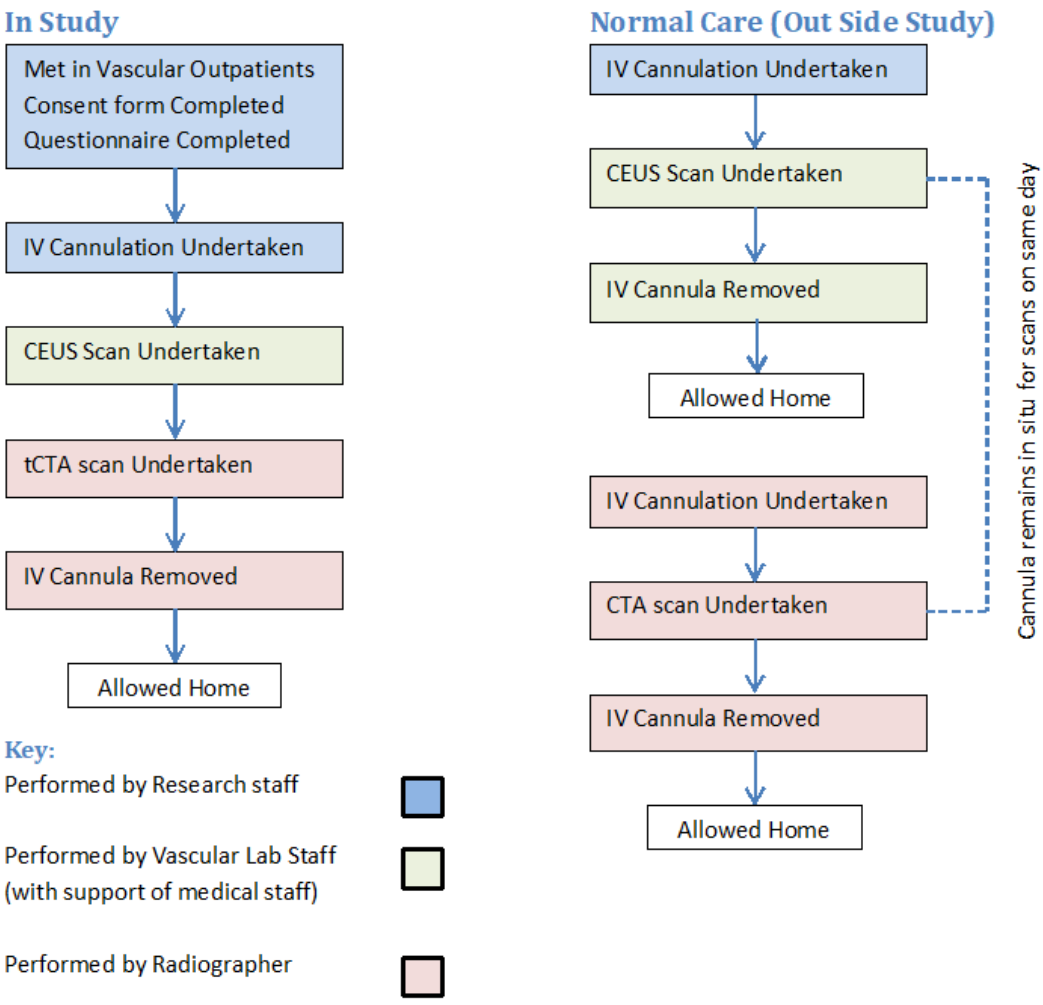
The consent process was commenced during a clinical contact. A verbal description of the study was given including what would be involved for the participant, as well as the potential risks and benefits for them. The participant information leaflet, Appendix 4 (page 236), and a consent form was left with the participant or posted to them and a time established for the study to re-contact them to confirm if they wish to participate.

The participant was re-contacted at the arranged time to confirm if they wish to participate. If they wish to participate a time/date was arranged for the study scans.

If they did not wish to participate, a CEUS and standard CTA was arranged as planned, outside the study. Figure 47 (page 133) depicts the patients flow through the study compared to normal care outside the study. All participant involvement was limited to a single day.

Participants were met in the outpatient department of LiVES by a study investigator on the arranged date of their scans. In a consultation room, confirmation of consent and wish to proceed was confirmed. All data were recorded onto a pro-forma, Appendix 5 (page 242). The initial questionnaire was completed by the investigator and height and weight recorded following consent.

Figure 47: Patient journey Inside/Outside Study



Flow diagram demonstrates patient flow inside and outside of the study.

3.3.4 Contrast Enhanced Ultrasound Scan

CEUS is performed in combination with a standard CDUS within LiVES. It is reported as a binary test yielding two values: presence or absence for each endoleak type. It is conducted by an experienced Clinical Vascular Scientist with extensive involvement in scans for EVAR surveillance. It is performed on a Philips IU22 ultrasound machine (Philips, Amsterdam, Netherlands), using the 2-5MHz abdominal curved array probe. Grey scale images of the aneurysm neck (when possible), iliac seal zones and maximum aneurysm dimensions are obtained and measured in maximum antero-posterior and medio-lateral dimensions. The echogenicity of thrombus within the aneurysm sac is noted. Using colour flow imaging and spectral Doppler, waveform characteristics and velocities are recorded in the common femoral arteries. The stent-graft is interrogated using colour and spectral Doppler to ascertain patency and flow haemodynamics of the neck, main body as well as both limbs. Any abnormalities in these parameters are reported. Colour Doppler is used to detect any endoleak. If present, its type, point of inflow, point of outflow and flow dynamics (using spectoral Doppler) are reported.

Optimum views of the area of concern are obtained, prior to contrast injection, using appropriate machine set ups and controls as determined by the operator. 2.4ml Sulphur Hexafluoride Microbubble Contrast (SonoVue™, Bracco, Milan, Italy) is injected followed by 10mls of sodium chloride 0.9%, the on-screen timer is started at the point of commencing the injection. Flow direction and filling time ideally should be determined and anatomy of the endoleak established by interrogation. Passive elimination of the contrast agent is allowed to occur and the process repeated for a second injection.

CEUS scan was reported by the performing vascular scientist to these data points, recorded in the data collection proforma, in addition to any clinically relevant points. The vascular scientist was blinded to the concurrent tCTA at the time of reporting, although was aware of the previous findings on EVAR surveillance. CEUS performed by multiple vascular scientists in the same sitting would have been desirable to allow inter-observer variability to be measured, this was not possible due to ethical concerns over multiple microbubble contrast injections. While these CEUSs were recorded for timings analysis, blind secondary reporting was not felt appropriate as image acquisition is user dependent and knowledge of probe position is an integral component to CEUS interpretation.

3.3.5 Time-Resolved Computer Tomography Angiography

tCTA was performed on a Siemens Definition AS+ scanner (Siemens, Munich, Germany). Participants were positioned supine with arms raised above their head. The contrast injector was connected to a 20G (or larger) IV catheter in an anterior cubital fossa vein. A standard topogram scan was performed. Unless not required, a non-contrast scan was performed. The maximum length that can be covered for the time resolution required is 27cm. This was centred over the EVAR stent-graft. Abdominal guides were placed at upper aspect of diaphragm and common femoral arteries for venous phase of scan. Abdominal aorta, just proximal to EVAR graft was selected as trigger area for time-resolved phases.

Contrast (Ioversol 64%) is injected, using an auto injector, at 4ml/s for 96mls. Participants were asked to adopt shallow breaths and not to hold their breath. The time-resolved phase was triggered by an increase in Hounsfield units (HU) >90 in trigger area. Phases occurred at 2, 4.5, 7, 9.5, 14.5, 19.5 and 24.5 seconds following the automatic trigger, these occurred in cranio-caudally acquisition, except the 5 and 7.5 second phases which occur caudo-cranially direction. The venous phase was taken in full inspiration and was acquired 75s following the trigger. Tube setting and calculated predicted radiation exposure are presented in Table 28 (Page 135).

Table 28: Tube setting and Radiation exposure for time-resolved and arterial phases of CT angiography

	Arterial phase (outside study)	Time-resolved phases (inside study)
Tube voltage	120	80
Tube Current (mA)	230 -(effective current–scanner automatically varies)	120
Scan Length (cm)	Variable (dependent on body length)	27
Number of Phases	1	7
Expected DLP	599.6*	552.3 (78.9 x 7 phases)

*Average DLP used for an arterial phase scan in all CT angiography scans in LiVES in month of July 2015. DLP= Dose Length Product.

All tCTA scans were reported by a single consultant vascular radiologist. This consultant was blinded to the results of the CEUS and collect data to the proforma,

Appendix 5 (page 242). It was reported as a binary test yielding two values: presence or absence for each type of endoleak.

Recruitment of participants, who were planned to undergo CTA in their care, and changing this to tCTA, meant that on average participants would not receive higher radiation exposure than they were already planned for Table 28 (page 135).

3.3.6 Outcomes

3.3.6.1 Primary Outcome

The primary outcome is:

- The predictive values of CEUS (index test) in comparison to tCTA (reference test) to detect stent-graft related endoleaks.

3.3.6.2 Secondary Outcomes

The Secondary outcomes are:

i. The rate and type of adverse events for CEUS and tCTA

ii. Predictive values of CEUS(index test) in comparison to tCTA (reference test) to detect:
   any endoleak
   type II endoleak

iii. Predictive values of both tCTA (index test 1) and CEUS (index test 2) in detecting:
   any endoleak
   type II endoleak
   graft-related endoleak
   in comparison to final endoleak diagnosis (reference standard), following any further investigations.

iv. Evaluate the association between CEUS temporal delay (difference between contrast in endograft and contrast in endoleak) and evaluate its ability to differentiate between of endoleak types.

v. Evaluate the association between “time for CEUS contrast in endoleak” to “time for tCTA contrast in endoleak” and assess potential as predictive tool, for optimum timing of CTA phases.

3.3.7 Statistical Analysis

3.3.7.1 Power Calculation

The power calculation was undertaken to a well described formula,[121] and showed the required sample size to be 74. This was calculated based on a prevalence of stent-graft related endoleaks of 11% as demonstrated on previous tCTA studies of endoleaks.[122] The sample size was based on a presumed sensitivity of 0.95, taken from previous meta-analysis[72 73] and a decision to tolerate confidence interval of ±0.15 in the outcome. This confidence interval was based on calculations of sample sizes at different confidence intervals (Table 29, page 137) and ability to recruit patients in a timely manner (Heading 3.3.2.1, page 132).

Table 29: Sample size required to show sensitivity of 0.95 to detected Type I and III Endoleak at given precisions of confidence interval.

Tolerable Confidence Interval Precision	Number participants required in study
+/- 0.1	166
+/- 0.15	74
+/- 0.2	42

3.3.7.2 Predictive Values

Predicative values (Sensitivity, specificity, positive predictive value and negative predictive value) were calculated along with binomial exact 95% confidence intervals. This was performed in RStudio v1.1.453 (RStudio, Inc., Boston, MA, USA) using DTComPair package v1.0.3. This performs McNemar test [123] and exact binomial test. Further it uses several methods to compute confidence intervals for differences in sensitivity and specificity. These methods are: generalised score statistic,[124] weighted generalized score statistic[125] and comparison of relative predictive values.[126]

3.3.7.3 Association and Predictive Modelling

Distribution of values was confirmed/refuted to be normal using graphical representations in the form of quantile-quantile plots. Following confirmation of normality or transformation to achieve normal distribution, associations was assessed with graphical analysis and appropriate further statistical testing of correlation within

the framework of logistic regression e.g. Pearsons test for linear correlations. If association could be established, then predictive modelling would be undertaken.

3.3.8 Full Code for Data Processing and Analysis

The full R code used to process and analyse these data is presented in appendix 6 (page 249).

3.3.9 Study Registration, Structure and Approvals

The study was prospectively registered on clinicaltrials.gov, a clinical trials registry, reference: NCT02688751.[127]

The Research Department of the Royal Liverpool University Hospital Hospitals NHS Trust granted full sponsorship (reference 5083). The study protocol was peer-reviewed by two clinical academics as part of the sponsorship application process. The trial was conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework. The main ethical issue raised by the study was the change in CT scan from standard care. Participants received a tCTA instead of standard CTA and were asked a small number of non sensitive questions, as outlined in the data collection proforma, Appendix 5 (page 242)

We felt this was ethically justifiable for 4 reasons;

1. Participants made an informed choice to participate in the study
2. The average radiation dose of a tCTA was predicted to be the same as a standard CTA
3. tCTA has a methodological superiority in endoleak detection compared to standard CTA in other institutions
4. If our hypothesis was proven it would produce evidence to support the use of CEUS instead of CTA which would reduce the use of potentially nephrotoxic contrast and ionising radiation within the EVAR surveillance population.

The study protocol was reviewed by and a favourable ethical opinion was obtained from the NHS Health Research Authority, National Research Ethics Service, North West – Preston Research Ethics Committee, reference 15/NW/0908. Annual progress and safety reports and final report at conclusion of the study were submitted to the sponsor and ethics committee.

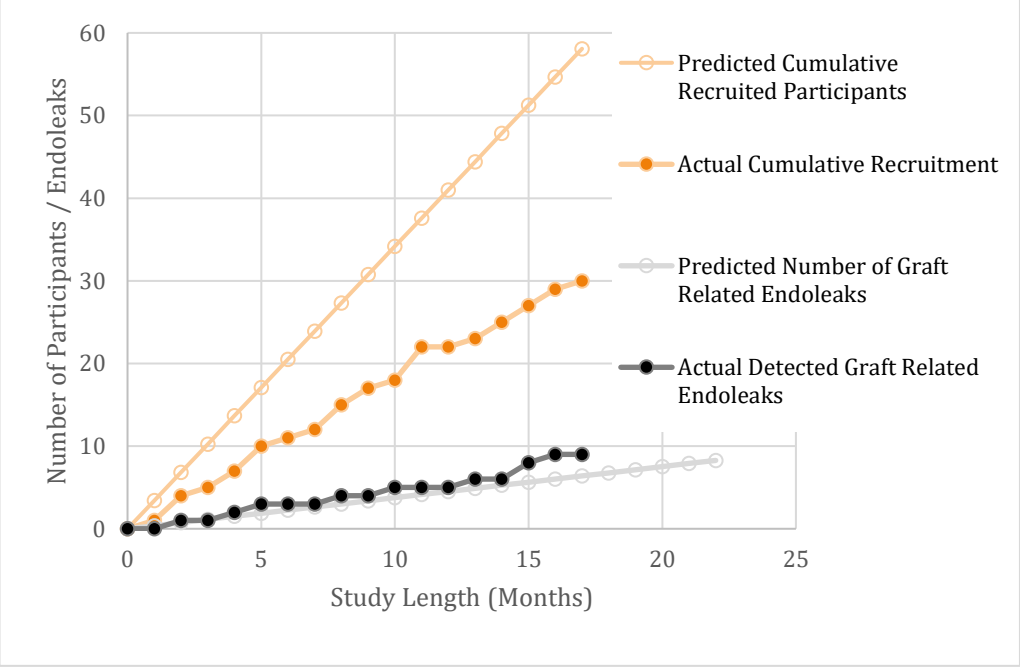
3.4 Results

A total of 36 patients were referred for inclusion in the study. 30 patients were recruited over 17 months. Of the 6 patients not recruited; 4 had a BMI over 30, 1 had embolization material present and 1 declined to participate. The complete data, from those who participated is presented in Appendix 5 (page 242).

3.4.1 Recruitment

The study was suspended, then stopped, before full recruitment due to slower than anticipated recruitment of participants, Figure 48 (page 139) and an interim analysis performed. This decision was informed by the fact that the incidence of graft-related endoleaks was significantly higher in the study participants than anticipated for the power calculations, 30% vs an anticipated 11%. Recruitment was running at 52% of the predicted rate which would have nearly doubled the studies length to achieve its recruitment target. As such in discussion with the studies sponsor recruitment was suspended once the target number of endoleaks was achieved. Due to time lag between scan and reporting one further patient was included following this being achieved.

Figure 48 : Predicted / Actual Recruitment and Graft-Related Endoleak Numbers in a Prospective Diagnostic Value of Imaging Modalities Study



Cumulative number of patients recruited and graft-related endoleaks detected over the study period with pre-study predictions for comparison.

3.4.2 Demographics

29 Males and 1 Female were recruited to participate. The mean age of participants at the time of operation was 75.6 years (range 62.9 – 88.3), the mean time elapsed between surgery and participation in the study was 4.2 years (range 0.1 – 11.8). The participants had EVAR stent grafts manufactured by :Medtronic® (Dublin, Ireland) 8 participants, W. L. Gore and Associates (Newark, Delaware, USA) 10 participants and Cook Medical (Bloomington, Indiana , USA) 12 participants. The mean BMI of participants was 25.8 (range 17.8 – 30.0). 37% had established Ischemic heart disease, but only 13% had an established diagnosis of cardiac arrythmia. 13 participants (43%) were fully active, 14 (47%) participants could not carry out heavy physical work but otherwise of good functional status and 3 (10%) participants were less able to perform daily tasks.

3.4.3 Primary Outcome

The findings on CEUS, tCTA and the diagnosis each participant were eventually clinically treated as are summarised in

Table 30 (page 140).

Table 30: Summary of Individual Participant Endoleak Findings

Participant ID	CEUS Endoleak Diagnosis	tCTA Endoleak Diagnosis	Final Clinical Diagnosis
7	Graft Related	Graft Related	Graft Related
9	Type II	Type II	Type II
14	Graft Related	Type II	Type II
46	NONE	NONE	NONE
48	Type II	Graft Related	Graft Related
57	Type II	Type II	Type II
59	Type II	Type II	Type II
70	Type II	Graft Related	Type II
75	Type II	NONE	NONE
83	Type II	Graft Related	Graft Related
85	NONE	NONE	NONE

95	Graft Related	Graft Related	Graft Related
184	Type II	Type II	Type II
205	Type II	Type II	Type II
289	Type II	Type II	Type II
301	Type II	NONE	Type II
357	Graft Related	Type II	Type II
409	NONE	NONE	Type II
486	Type II	Type II	Type II
533	Type II	Type II	Type II
579	Graft Related	Graft Related	Graft Related
660	Type II	Type II	Type II
679	Type II	Type II	Type II
705	Type II	Type II	Type II
709	Type II	Type II	Type II
750	Type II	Type II	Type II
760	Graft Related	Graft Related	Graft Related
774	Type II	Type II	Type II
876	Type II	Graft Related	Graft Related
879	Graft Related	Graft Related	Graft Related

3.4.3.1 Predictive Values of CEUS to Detect Graft-Related Endoleak, with tCTA as the Reference Standard

A total of 9 graft-related endoleaks were diagnosed on tCTA giving a prevalence of 30%. 1 type Ia, 2 type Ib and 6 type III endoleaks were detected. 7 graft-related endoleaks were detected on CEUS: 4 type Ia, 1 type Ib, and 2 type III endoleaks but not all in the same participants. This provides the diagnostic values for CEUS to detect graft related endoleaks shown in Table 31 (page 142).

Table 31: Diagnostic Values of CEUS (Index) Compared to tCTA (Reference) in Detecting Graft-Related Endoleaks

	Estimate	95% Confidence Interval
Sensitivity	0.56	0.23 – 0.88
Specificity	0.90	0.78 – 1.00
Positive Preditive Value	0.71	0.38 – 0.96
Negative Predictive Value	0.82	0.67 – 0.98

3.4.4 Secondary Outcomes

3.4.4.1 Adverse Events for CEUS and tCTA

No participant suffered any serious adverse event while undergoing either CEUS or tCTA. One participant intravenous cannula occluded after the first injection of contrast for CEUS and on attempting the second injection the raised pressure cause by the occlusion ruptured the remaining microbubbles in the contrast rendering their second run non-diagnostic. The patient suffered no ill effects and the first run was diagnostic, so all required information was obtained for the participant's ongoing care.

3.4.4.2 Predictive Values of CEUS to Detect any Endoleak, with tCTA as the Reference Standard

In total there were 5 participants who had no endoleak detected on tCTA (83% prevalence of endoleaks). 2 of these participants did have a type II endoleak detected on CEUS, 3 participants had no endoleak detected on either modality. These filled at 16 and 50 seconds after contrast reached the graft, meaning that they may have not been detected on tCTA due to the specific tCTA protocol used was focused on detecting graft-related endoleaks. The diagnostic values for CEUS to detect any endoleak are shown in Table 32 (page 143).

Table 32: Diagnostic Values of CEUS (Index) Compared to tCTA (Reference) in Detecting Any Endoleak

	Estimate	95% Confidence Interval
Sensitivity	1.00	1.00 – 1.00
Specificity	0.60	0.17 – 1.00
Positive Preditive Value	0.93	0.83 – 1.00
Negative Predictive Value	1.00	1.00 – 1.00

3.4.4.3 Predictive Values of CEUS to Detect Type II Endoleak, with tCTA as the Reference Standard

16 participants who did not have a graft related endoleak had a type II endoleak, on tCTA, giving a prevalence of 53%. The diagnostic values for CEUS to detect a type II endoleak are shown in Table 33 (page 143).

Table 33: Diagnostic Values of CEUS (Index) Compared to tCTA (Reference) in Detecting Type II Endoleaks

	Estimate	95% Confidence Interval
Sensitivity	0.875	0.71 – 1.00
Specificity	0.57	0.31 – 0.83
Positive Preditive Value	0.70	0.50 – 0.90
Negative Predictive Value	0.80	0.55 – 1.00

3.4.4.4 Predictive Values of CEUS and tCTA to Detect Graft-Related Endoleak, with Final Diagnosis as the Reference Standard

A total of 8 participants (prevalence 26%) were treated on an ongoing basis with graft-related endoleaks. One participant had a type III endoleak diagnosed on the tCTA but had a multiplanar DSA which failed to demonstrate the type III endoleak. The DSA instead showed a lumbar type II endoleak at the same anatomical position. The participant was observed, and the aneurysm failed to demonstrate any further growth. Of the remaining graft-related endoleaks diagnosed on tCTA 3 were confirmed on re-intervention (1 DSA and 2 open surgery) and 5 were not intervened on (1 patient declined intervention, 2 patients unfit for intervention, 2 patient observed as growth rate

slow and good seal zone length). This demonstrated the diagnostic values of CEUS and tCTA compared to the best working diagnosis used to treat patients shown in Table 34 (page 144).

Table 34: Diagnostic Values of CEUS (Index 1) and tCTA (Index 2) compared to Final diagnosis (Reference) in Detecting a Graft Related Endoleak

	CEUS Estimate (95% CI)	tCTA Esitimate (95% CI)
Sensitivity	0.625 (0.29 – 0.96)	1.00 (1.00 – 1.00)
Specificity	0.91 (0.79 – 1.00)	0.95 (0.87 – 1.00)
Positive Preditive Value	0.71 (0.38 – 1.00)	0.89 (0.68 – 1.00)
Negative Predictive Value	0.87 (0.73 – 0.98)	1.00 (1.00 – 1.00)

3.4.4.5 Predictive Values of CEUS and tCTA to Detect any Endoleak, with Final Diagnosis as the Reference Standard

2 endoleaks seen only on CEUS (not tCTA) were deemed by the MDT to be sufficiently well visualised to be secure as a diagnosis. Giving a final prevalence of endoleaks in the participants of 90%. The diagnostic values of CEUS and tCTA when final diagnosis was used as the comparator are presented in Table 35 (page 144).

Table 35: Diagnostic Values of CEUS (Index 1) and tCTA (Index 2) compared to Final diagnosis (Reference) in Detecting Any Endoleak

	CEUS Estimate (95% CI)	tCTA Esitimate (95% CI)
Sensitivity	0.96 (0.89 – 1.00)	0.93 (0.83 – 1.00)
Specificity	0.67 (0.13 – 1.00)	1.00 (1.00 – 1.00)
Positive Preditive Value	0.96 (0.89 – 1.00)	1.00 (1.00 – 1.00)
Negative Predictive Value	0.67 (0.13 – 1.00)	0.60 (0.17 – 1.00)

3.4.4.6 Predictive Values of CEUS and tCTA to Detect Type II Endoleak, with Final Diagnosis as the Reference Standard

The final diagnostic value of CEUS and tCTA are displayed in Table 36, page 144.

Table 36: Diagnostic Values of CEUS (Index 1) and tCTA (Index 2) compared to Final diagnosis (Reference) in Detecting Type II Endoleaks

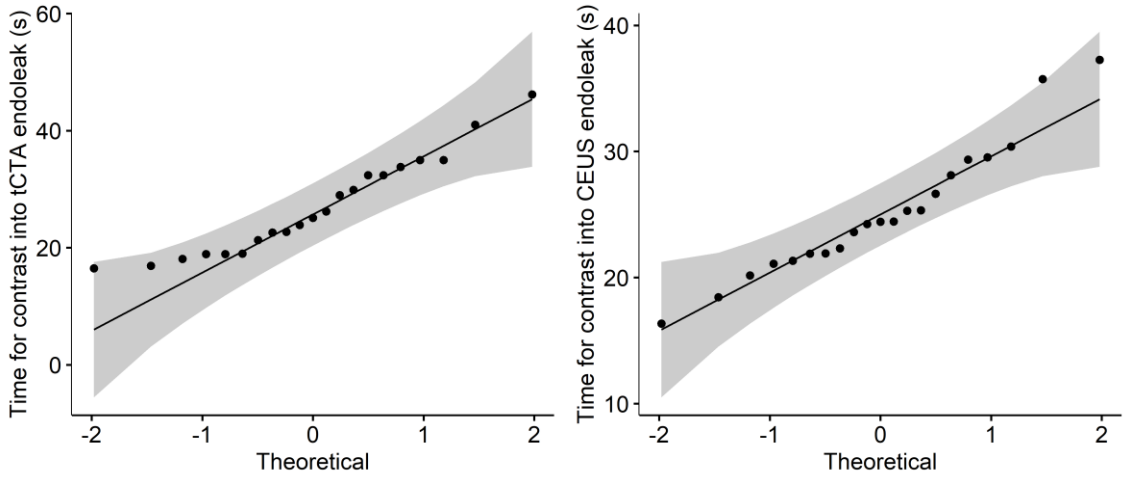
	CEUS Estimate (95% CI)	tCTA Esitimate (95% CI)
Sensitivity	0.84 (0.68 -1.00)	0.84 (0.68 – 1.00)
Specificity	0.64 (0.35 – 0.92)	1.00 (1.00 – 1.00)
Positive Preditive Value	0.80 (0.62 – 0.97)	1.00 (1.00 – 1.00)
Negative Predictive Value	0.70 (0.42 – 0.98)	0.79 (0.57 – 1.00)

3.4.4.7 Evaluate the Association Between "Time For CEUS Contrast In Endoleak" to "Time For tCTA Contrast In Endoleak" and Assess Potential as Predictive Tool for Optimum Timing of CTA Phases.

Distribution of time for contrast be seen in endoleak on both tCTA and CEUS was assessed using Q-Q plots demonstrated in Figure 49 (page 145).

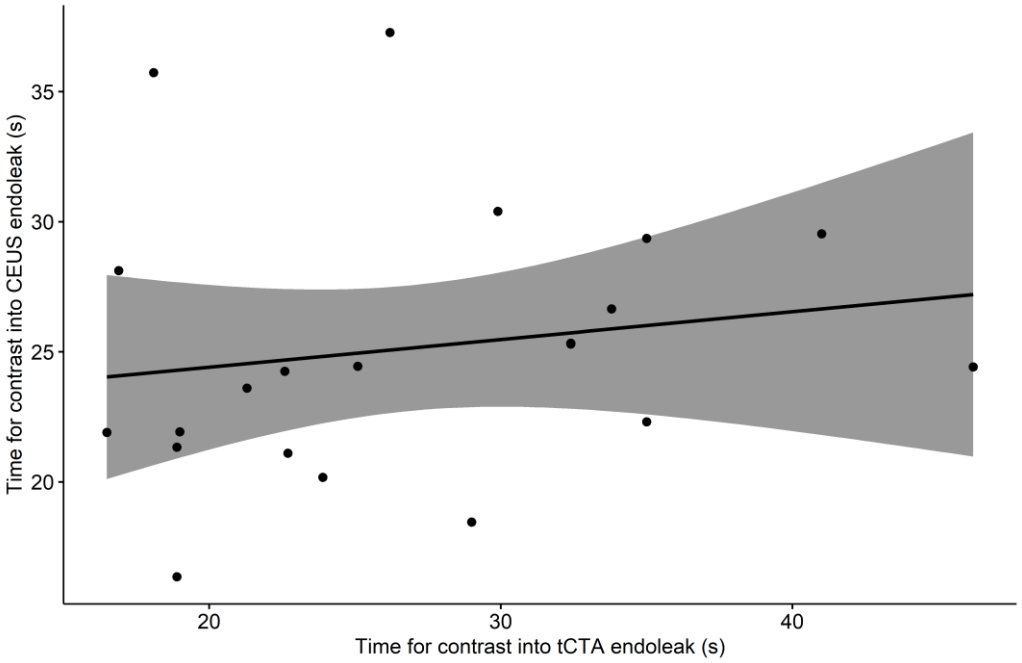
This demonstrated normality of the two distributions and therefore graphical assessment of association was undertaken, Figure 50 (page 146). No association of any form was evident. A best fit linear correlation was fitted, Figure 50 (page 146) and a Pearson correlation coefficient calculated of R=0.17 (p=0.46) was calculated. This confirmed no linear correlation existed.

Figure 49: Quantile-Quantile plots of the distribution of Time for contrast to be seen in endoleaks on both tCTA (left) and CEUS (Right)



Q-Q plot of time for contrast to arrive into endoleak on tCTA & CEUS. Both plots demonstrate approximal linearity within the confidence interval, suggesting both are normally distributed.

Figure 50: Association plot of time for contrast to be seen in an endoleak on tCTA vs CEUS, best fit linear correlation line with 95% confidence interval superimposed.



Scatter plot of paired times for contrast to arrive in to endoleak on tCTA & CEUS, demonstrating no apparent pattern of relationship. Solid line and grey confidence interval represent a best fit linear correlation demonstrating significant numbers of points outside confidence interval and therefore poor fit of model.

3.4.4.8 Enhancement Data for EVAR Lumen and Endoleaks from tCTA

There is large variability between participants in enhancement patterns, this is due to: 1) The large variability in the time to trigger the scan (range 14.5-34.9 s, interquartile range 18.4-22.6 s and median 20.5 s) and 2) The variability in peak opacification e.g. in EVAR lumen opacification (range 315-705 HU, interquartile range 430-508 HU, median 468.5 HU).

Summaries of these raw data are presented in Table 37 (page 147) and Table 38 (page 147).

Table 37: Summary of contrast evident in different findings on time-resolved CTA by time

	Time Since time-resolved phase of CTA triggered (s)							
	2	4.5	7	9.5	14.5	19.5	24.5	75
Contrast evident in EVAR lumen	100%	100%	100%	100%	100%	100%	100%	100%
Contrast evident in graft related endoleak (if present)	100%	100%	100%	100%	100%	100%	100%	100%
Contrast evident in Type II endoleak (if present)	19%	33%	52%	67%	86%	86%	95%	100%

Table 38: Summary of timing of peak opacification of different findings on tCTA by time

	Time Since time-resolved phase of CTA triggered (s)							
	2	4.5	7	9.5	14.5	19.5	24.5	75
Peak opacification in EVAR lumen	0%	3%	0	33%	37%	33%	0	0
Peak opacification in graft related endoleak (if present)*	12.5 %	0%	0%	0%	0%	37.5 %	50%¥	0%
Peak opacification in Type II endoleak (if present)	0%	5%	5%	0%	0%	10%	67%¥	14%¥

* One participant recorded equal peak opacification at two subsequent time points

¥ these endoleaks had their highest enhancement recorded in the last time point of the time-resolved phase or in the venous phase meaning that potentially the peak enhancement may have fallen any-time in the 50s time elapse between these points.

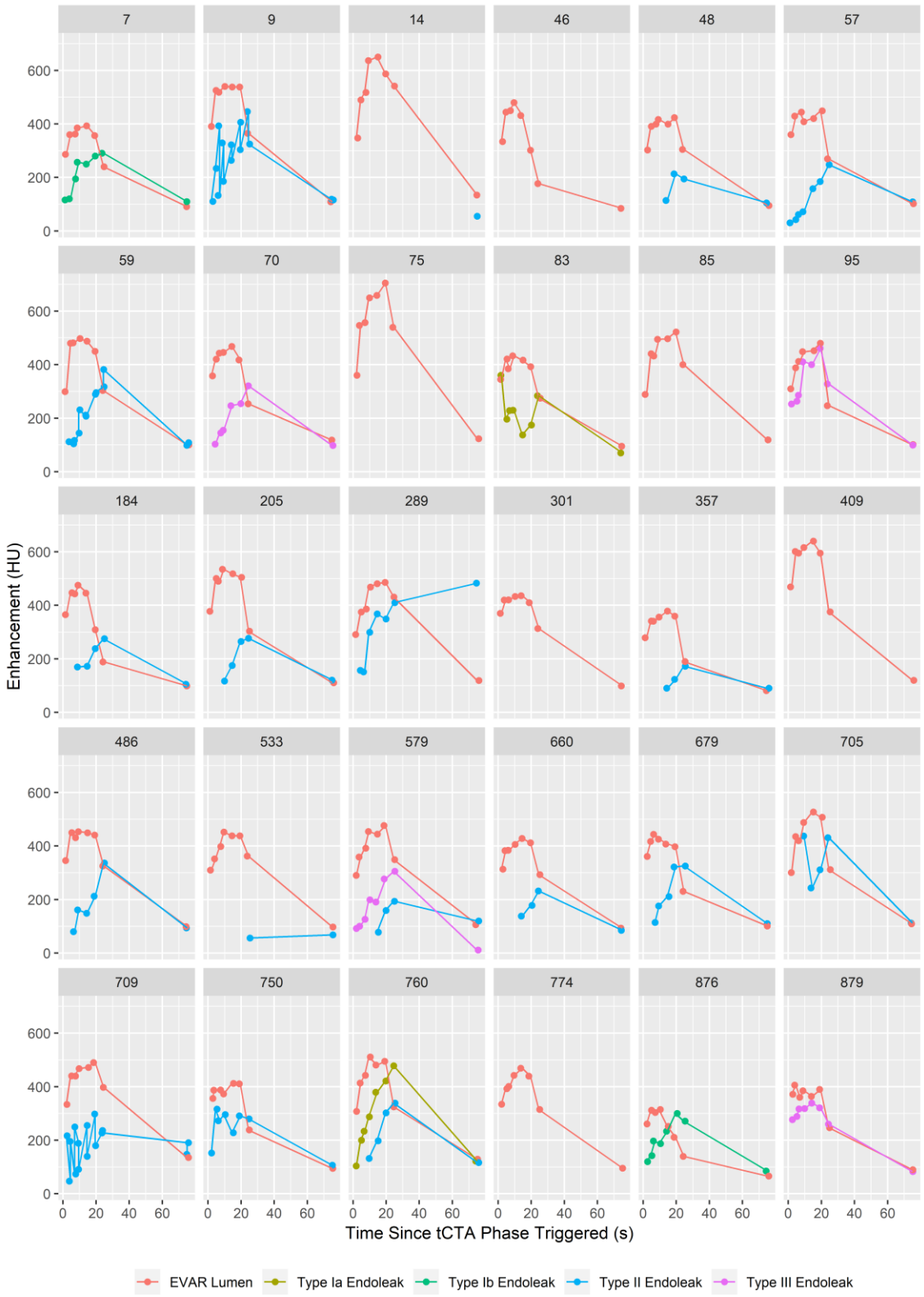
The individual enhancement patterns of the EVAR stent-grafts and any evident endoleaks seen on tCTA for each participant are presented in visual form in Figure 51 (page 149).

All participant information for enhancement of each endoleak type and stent-graft lumen can then be adjusted for the time for the time-resolved phase to be triggered and condensed into single scatter plots for each enhancement type, Figure 52 (page 149).

These data can be transformed to allow a 2nd degree (quadratic) polynomial distribution best fit line, with confidence intervals, to be over laid. Endoleak type can be maintained but graphs are condensed to “class” of enhancement, Figure 53 (page 150).

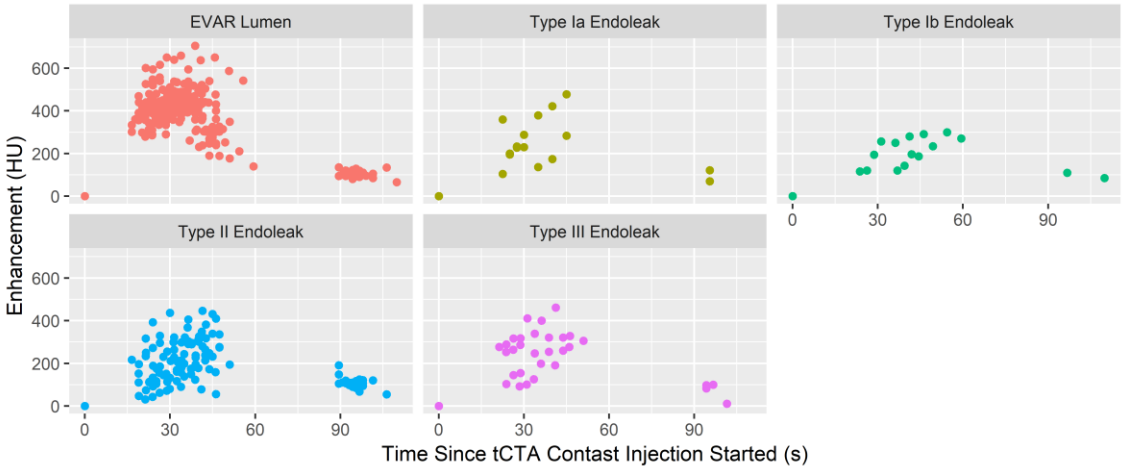
These data can then be condensed into class based best fit lines and displayed side by side, Figure 54 (page 151).

Figure 51: Enhancement Patterns of EVAR Stent-Grafts and Endoleaks on tCTA for Each Study participant



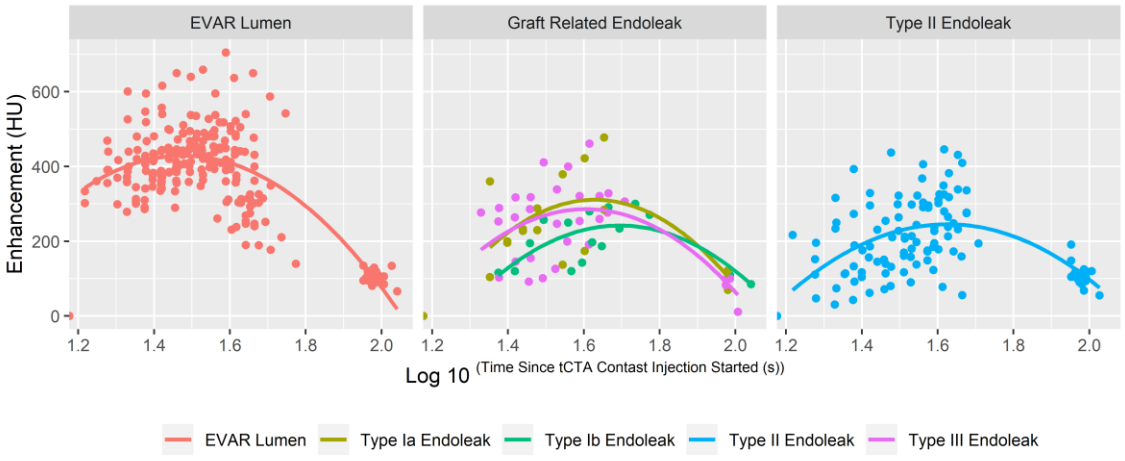
Filling (enhancement) patterns over time of differing endoleak types in 30 time-resolved CTA studies in different patients.

Figure 52: Perfusion Data Points By Enhancement Type From Start Of tCTA Contrast Injection



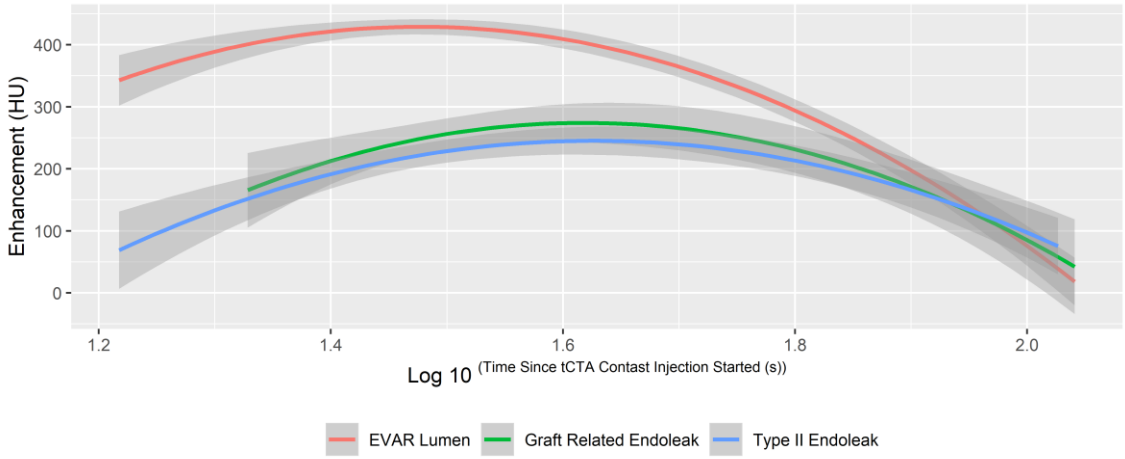
Combined enhancement values of 30 time-resolved CTA studies in different patients, divided in to plots by endoleak type.

Figure 53: Perfusion data for different enhancement objects with best fit mean lines



Combined enhancement values of 30 time-resolved CTA studies in different patients, divided into plots by endoleak class. With individual endoleak types in separate colours with best fit lines to aid interpretation.

Figure 54: Best fit mean enhancement for different enhancement object classes



Best fit lines by endoleak class from combined enhancement values of 30 time-resolved CTA studies in different patients. Demonstrates near identical enhancement pattern of graft-related and type II endoleaks.

3.4.5 Radiation Dose Data

The radiation exposure and estimated absorption within the study, Table 39 (page 152), was lower than those calculated in the preparation of the study, Table 28 (page 135). This discrepancy may be accounted for by the selection criteria of individuals with a BMI below 30. The DLP for the time-resolved phases, 497mGy/cm, was essentially identical for all participants and lower than the mean value of the venous phase which replicated settings that would be have been used for a single arterial phase. The venous phase DLP had a wide range from 348 – 936 showing that some, lower BMI, patients had a slight increased radiation exposure from participation in the study due to a lack of ability to actively vary tube current within time-resolved phases, to manage patient radiation dose. This possibility was detailed in the participant information leaflet, Appendix 4 (page 236).

Table 39: Tube Settings and Radiation Exposure for Time-resolved and Venous Phases of CT Angiography Within Study

	Time-resolved phase(s) Mean (Range)	Venous phase Mean (Range)
Tube voltage (keV)	80 (-)	120 (-)
Tube Current (mA)	120 (-)	190 (214 – 270)
Number of Phases	7	1
CTD/Vol (mGy/L)	18.01 (17.99-18.04)	12.91 (8.38 – 18.22)
Total DLP (mGy/cm)	497 (496-498)	562 (348 – 936)

3.5 Discussion

This study demonstrates the diagnostic values of CEUS to detect and characterise endoleaks compared to a methodologically superior reference standard than all the currently published literature. Its prospective blinded nature along with compliance with the STARD principles likely make it the most rigorous study performed in this area. It contains the largest sample of graft related endoleaks in any CEUS diagnostic values study.

3.5.1 Power Calculation

The power calculation was based on two assumptions. These two assumptions: a prevalence of graft related endoleaks of 11% and a sensitivity of CEUS to graft related endoleaks of 95%, were informed by the literature but were ultimately inaccurate.

The prevalence of graft-related endoleaks was assumed to be 11% based on a Sommer et al's previous tCTA study.[122] Sommer et al recruited their participants from a pool of patients at increased risk of having an endoleak, which they defined as "The patient was suspected of having an endoleak at a previous imaging study, the patient was known to have postoperative endoleaks, or the patient was at high risk for endoleaks because of atypical anatomy (ie, aneurysmal widening of the iliac arteries or a short aortic neck for stent placement)." 46 of their participants were patients with infra-renal EVAR, 5 had a graft related endoleak to give the prevalence of 11%.

In this study we recruited participants at increased risk of graft related endoleaks based on "the participant was having initial post-op imaging and had a type I/III endoleak on

completion angiography OR participants who have had aneurysm expansion or type I/III endoleak suspected on standard surveillance (CDUS) and are planned for a CTA and CEUS".[118] In this study 9 graft related endoleaks were diagnosed in the 30 patients who participated in this study, giving a prevalence of 30%.

The difference in methodology in recruiting patients at increased risk of endoleak almost certainly account for the difference in prevalence. Sommer et al.'s stated aim was to recruit patients at risk of [any] endoleak, in contrast this study was more focused, and aimed to recruit participants at high risk of, the more clinically important, graft related endoleaks. If we had also recruited patients without aneurysm expansion but type II endoleaks present on CDUS we would likely have had a graft related endoleak prevalence much more similar to that of Sommer et al. but conversely had to recruit more patients. This however would not have significantly bolstered the value of the study regarding its primary outcome. Recruiting such patients would have also had ethical dilemmas as they would not normally have a CTA in their routine care which we would then be subjecting them to. Finally, there would have been additional financial cost of recruiting such patients and performing tCTA that would not have otherwise been performed.

The sensitivity of CEUS for the power calculation was predicted to be 95% based upon Karthikesalingam et al.'s meta-analysis.[73] Karthikesalingam et al.'s 2012 meta-analysis is the only one that differentiates between any endoleak and graft related endoleaks in its analysis but does have other methodological flaws such as including all methods of CEUS scanning under one analysis, see section 1.3.7 (page 21). A secondary analysis performed of CEUS as the reference standard for CTA acknowledges the potential issues of presuming CTA to be a superior modality. The use of a potentially superior comparator in the form of tCTA should perhaps have prompted a lowering of the assumed sensitivity, however there would have been no way to quantify the extend of this. The final sensitivity 56% is much lower than would have been predictable.

If the incidence of graft related endoleaks of 30% had been predictable and the tolerated confidence interval of +/- 15% had been maintained the power calculation would have suggested a sample size set out in Table 40 (page 153), for various sensitivities.

Table 40: Suggested sample sizes by sensitivity from power calculation based on prevalence of 30% and tolerated confidence interval of +/- 15%.

Assumed Sensitivity	Number participants required in study
95%	28
75%	107
55%	142

If this had been used for initial calculation and the sensitivity was thought likely to be 95% we would have recruited sufficient patients for analysis e.g. >28 participants.

Assuming the sensitivity in the primary outcome is correct (despite its wide confidence interval) any future study which wished to show the sensitivity of CEUS to detect and correctly characterise graft related endoleaks to +/- 15% sensitivity would be required to recruit in excess of 140 participants while maintaining a prevalence of graft related endoleak rate of 30% within the study population.

3.5.2 Recruitment

Recruitment to the study averaged 1.8 participants a month, instead of the predicted 3.4 participants. This prediction was based upon the calculation that 8.4% of CDUS scans show results that would require further investigation, making that patient a potential participant. This was multiplied by the average number of CDUS scans performed in the LiVES service each year of 590. This figure based on data, Table 27 (page 132), that included a year with almost double the number of scans in other years. If this year had not been included a more realistic 513 CDUS scans a year could have been included. This alone would have reduced the prediction for recruitment down to 3 participants/month. A further factor that was not taken into account was that many of the CDUS findings were in the same individual patients who were having repeated surveillance scans. This was particularly important as the planned recruitment schedule covered more than 12 months, which is the normal interval for standard EVAR surveillance in LiVES. Meaning that after 12 months many patients who had already participated in the study were having repeated findings that would have made them eligible again.

This slow recruitment was offset by the much higher than anticipated prevalence of graft related endoleaks which ultimately lead to the decision to perform an interim analysis once the target number of graft related endoleaks had been seen. The delay between tCTA scan and report ultimately meant we had 1 over target graft-related

endoleaks, as 2 occurred in quick succession at the end of recruitment. Interim analysis showed a much lower than expected sensitivity of CEUS. When the above power calculations, Table 40 (page 153), were performed it was apparent that recruiting further participants was not going to significantly change the scientific value of the results of the study. As such the study was terminated early. This decision was taken in the context of the slow recruitment to date meaning that achieving initial sample size or even larger samples based upon a change to the protocol was not practical with the resources and time available. It would represent the largest sample of paired CEUS and CTA (of any type) samples if included in the meta-analysis of note.[73]

3.5.3 Study Methodology and Limitations

This study was the first to compare CEUS to tCTA in a blinded prospective comparative study. As such it is the first to compare CEUS to the methodologically superior tCTA as opposed to standard CTA. As such its results may more closely represent the true diagnostic values of CEUS compared to the gold standard of multiplanar DSA. It is methodologically superior to many published studies in that it was a prospective and blinded study that was designed to adhered to the STARD standards.[119] The fact that all participants had the paired scans within 2 hours of each other has also not been achieved by any other study published in the literature and all but removed changing findings as a confounding factor. The prospective publication of the protocol, [118] before analysis, is also a quality indicator not achieved by any other study in this area. Finally the primary outcome was set as the diagnostic values for the detection and correct characterisation of graft-related endoleaks which is the most clinically relevant. Most other studies have examined simple detection of any endoleak as the primary outcome, with only a proportion looking at endoleak characterisation as a secondary outcome. Any endoleak detection is interesting but is unlikely to drive a change in clinical decisions without aneurysm growth which can accurately be shown on CDUS and would prompt further investigation without endoleak detection in LiVES practice.

tCTA has not been proven to be superior to CTA, it is however a logical methodological assumption. It would be unethical to undertake such a comparison due to the need to double expose patients to the contrast and radiation of these tests. No study has compared the diagnostic values of any modality (CDUS, CEUS, CTA or tCTA) compared to multi-planer DSA. tCTA is demonstrated to be a strong diagnostic test in

this study compared to final diagnosis but is not perfect as it mischaracterised an endoleak compared to subsequent DSA examinations. This supports, but does not prove, the hypothesis that CTA would also be inaccurately characterising endoleaks as it has less haemodynamics information to deduce endoleak character from.

The single individual interpreting and reporting of both tCTA and prevented the inter-reporter variability being explored. Both CEUS and tCTA were reported by experienced personal in a large volume tertiary centre that regularly undertake examinations in patients with such conditions. An equal number of CEUSs were performed and reported by 3 different individuals, all of whom have in excess of 5 years experience of CEUS examinations in post EVAR patients.

The single centre nature of the study and the underlying small sample also limit the scientific impact of this study.

Finally the change to the protocol to allow interim analysis which lead to termination of the study could have introduced bias into the results. Although the decision making behind this was logical and informed by the information available it was not envisaged in the study protocol. The decision to terminate the study was based upon valid ethical consideration that enrolling further participants would add little scientific value. Given the power calculation included such an assumption about prevalence of the disease future studies should include an analysis to allow adjustment of sample size based on actual prevalence in the study population. If such a protocol had existed this study would have re-calculated its sample size to be 28. And the study would have undertaken analysis as a completed study not an interim analysis that led to the early conclusion of the study.

3.5.4 Outcomes

3.5.4.1 Graft Related Endoleaks

The primary outcome: diagnostic values of CEUS to detect graft-related endoleaks, Table 31 (page 142) were markedly lower than expected. Sensitivity is the characteristic most important in these diagnostic values as a missed diagnosis of graft related endoleak may result in EVAR treatment failure and ultimately patient death. As such higher sensitivity at the expense of specificity is likely preferable. The sensitivity of 0.56 (95% CI, 0.23 – 0.88) is far below any acceptable level for a diagnostic test or surveillance imaging modality for such a diagnosis. Even if the small sample size has

lead to a sampling error that has given a lower than true value, the highest value in the 95% confidence interval is below that of any reported study. The methodological superiorities of this study compared to other published studies and the relatively large number of relevant findings compared to published literature mean that the accepted sensitivity of CEUS to detect graft related endoleaks must be questioned.

The sensitivity demonstrated in this study is lower than reported in the majority of the literature and may simply be a result of the improved comparator standard, tCTA, over previous studies which used CTA. This is reinforced by the comparison of both CEUS and tCTA to eventual final MDT diagnosis, Table 34 (page 144), following gold standard imaging (multi-planar DSA) of some patients and serial CDUS of others. The CEUS sensitivity for this diagnosis is 0.625 (95% CI 0.29 – 0.96) and for tCTA is 1.00 (95% CI 1.00 – 1.00). This confirms the hypothesised methodological benefits of tCTA as its perfect Sensitivity shows that even with all other information available to make the final diagnosis no further graft-related endoleaks were confirmed. The improved but still lower than anticipated CEUS sensitivity is in fact due to a single change in final diagnosis away from graft related endoleak to type II endoleak following a DSA examination.

Specificity of CEUS is shown, Table 31 (page 142), to be only slightly poorer than most of the literature. This is less concerning as false positive results following a surveillance / pragmatic diagnostic test can be resolved by gold standard imaging assuming the test produces tolerable level of false positives (specificity). The specificity results are similar between CEUS and tCTA when compared to final MDT diagnosis, Table 34 (page 144). If there is an inverse relationship between sensitivity and specificity it is reassuring that these are closely match suggesting a similar “threshold to diagnosis” has been applied during the study. This threshold in current clinical practice in LiVES should likely be moved towards higher sensitivity with a converse lowering of sensitivity in CEUS examinations.

Positive and negative predictive values have limited generalisation as they are influenced by prevalence of the condition being diagnosed. The high prevalence caused by highly selective criteria mean that these values have limited relevance to a generalised EVAR surveillance population. Predictive values calculated using a prevalence figure obtained by another form of imaging (not tCTA) would likely be misleading to present.

3.5.4.2 Any Endoleak

The perfect sensitivity 1.0 (95% CI 1.0-1.0) to detect any endoleak on CEUS compared to tCTA, Table 32 (page 143) and near perfect sensitivity 0.96 (95% CI 0.89-1.0) compared to final diagnosis, Table 35 (page 144), fit with existing literature. It is also a logical extension of our understanding of modern CEUS. Contrast is often seen in an endoleak in dynamic filling, however it is not always possible to visualise the point of origin, and even when seen this is seen in 2D preventing full 3D localisation of inflow point. This potentially limits the characterisation of the endoleak but contrast all but guarantees its visualisation. Therefore sensitivity to detect an endoleak is very high but sensitivity to correctly characterise it as graft related is poorer.

tCTA sensitivity 0.93 (95% CI 0.83 – 1.00) compared with final diagnosis was slightly lower than that of CEUS. Again this is logical as the protocol of the tCTA was designed to detect graft-related endoleaks and did not include a very delayed venous phase to detect slow filling type II endoleaks. The MDT final diagnosis accepted that some endoleaks were adequately seen solely on CEUS to warrant diagnosis as there was no corresponding tCTA phase, so depressing tCTA sensitivity. Some endoleaks seen solely on CEUS were not seen on corresponding phases of tCTA and as such the MDT was unable to confirm the diagnosis which, in turn, depressed the specificity of CEUS compared to final diagnosis, Table 35(page 144).

3.5.4.3 Type II Endoleaks

The diagnostic values for CEUS compared to tCTA, Table 33(page 143) and CEUS/tCTA compared to final diagnosis, Table 36 (page 144) are of limited extra value but were presented for completeness. They are essentially a reversal of the value for graft related endoleaks as any mis-characterisation between the classes of endoleaks subtracts from different elements of the diagnostic values.

The diagnosis of type II endoleak is of limited clinical value unless graft related endoleak can be confidently excluded and aneurysm growth can confidently be confirmed.

3.5.4.4 Correlation Data

This study did not demonstrate a correlation between timing information observed on CEUS and tCTA. This would have potentially been clinically useful as patients undergoing CEUS before CTA could have then potentially have had the time of their CTA phases tailored according to the information available on CEUS.

These differences likely arise as a result of the differences in contrast medium and volume and the effect this ultimately has on infection time. CEUS is a small bolus that is completely infected very rapidly and therefore likely arrives in peak concentration over a small number of cardiac cycles. tCTA however has a much slower injection of contrast (due to volume) that means the contrast arrives over a significantly longer period / number of cardiac cycles and therefore takes a much more variable period to reach detectable concentrations. We can further hypothesis this variability will be worsened by different participants various cardiac outputs, intra-vascular volumes and the systemic vascular resistance within the lumens to and through the endoleaks in question.

3.5.4.5 Perfusion Data

The haemodynamics and often complex anatomy of endoleaks make the interpretation of these data complex.

It is known that type II endoleaks can take several minutes to fill following CT contrast injection. The time-resolved CTA protocol used in this study was specifically designed to capture graft-related endoleaks so does not fully demonstrate all the haemodynamic characteristics of type II endoleaks that may be required to fully inform future CT protocol design.

tCTA sacrifices some “on screen” resolution in each phase to allow more phases to be captured for the same radiation exposure. The premise being that the temporal or haemodynamic information gained about the endoleak provides more information to characterise any endoleak than the potential loss in anatomical information from the reduced resolution. This is further mitigated by the use of standard venous phase within tCTA that allows anatomical information to be defined as normal on screen resolution. Not all phases on tCTA add significant haemodynamic information and if they could be further rationalised/reduced the on screen resolution of tCTA could be improved so regaining some of the potentially sacrificed anatomical information.

The objectives of performing a CTA vary depending on the situation but may include

1) Aneurysm size measurement (that does not require contrast and can be performed on any phase with or without contrast)
2) Assessing the length and quality of the seal zones, best performed with a high opacification of aortic lumen

3) Assessing for presence/absence of any endoleak – best performed with the highest opacification of the endoleak possible
4) Characterising an endoleak as potentially graft related – best done by fully defining its anatomy (as above) and haemodynamics (defining its inflow as well as full anatomy)

These data presented in Table 37(page 147) and Table 38 (page 147) demonstrate that objective 1 can be achieved at any time point, objective 2 by a phase at 14.5s following trigger, objective 3 by a phase between 14.5-19.5s for graft related endoleaks and between 19.5 and 75s for type II endoleaks and objective 4 by at least 1 phase around 2s for graft related endoleaks and multiple phases would be required to definitely capture all type II endoleaks.

All this could potentially be achieved by a phase at 2s (to observe the inflow/haemodynamics) of graft-related endoleaks +/- a phase 2.5-5s later, a phase at 19.5s (to get peak opacification of graft related endoleaks) and very near peak opacification of aortic lumen to assess seal zone length and quality, a “late” venous phase up to 75s after trigger to capture type II endoleaks not seen on earlier phases and to fully define the anatomy of endoleaks not fully visualised previously.

It is therefore possible to get the majority of the useful haemodynamic information from a tCTA with only 3 or 4 phases. Minimising the need to reduce resolution by decreasing radiation dose.

If only one phase is to be performed (as the haemodynamic information is not felt to warrant the extra radiation exposure) then it should be at 19.5 seconds following trigger as this will get peak graft-related endoleak opacification in 50% of cases (100% will be opacified to some extent), more than adequate EVAR lumen opacification to assess seal zones and 86% of type II endoleaks will be opacified. The selection criteria for this study may mean that the endoleaks represented, and therefore their haemodynamics, may not be representative of a general surveillance population.

3.6 Summary

This study has shown the sensitivity of CEUS to detect graft related endoleaks to be significantly lower than previous reported. It is hypothesised that this is due to CEUS being compared to a superior reference standard of tCTA. It has confirmed CEUSs sensitivity to detect any endoleaks is equivalent to the tCTA protocol in this study.

CEUSs weakness remains differentiating between endoleak types or classes.

This study was carried out to more rigorous scientific standards than the majority of the published literature and this study contains more graft-related endoleaks than any other published study. It adds valuable information to the published literature which should influence the choice to use CEUS in clinical practice. CEUS likely does not have the diagnostic abilities to reliably differentiate endoleak classes of types but is a highly reliable way to diagnosis the presence of an endoleak in the absence of a known cause for aneurysm growth.

The perfusion patterns of endoleaks seen on tCTAs within this study can be used to improve the timing of phases on tradition single or multi-phase CTA to allow optimum imaging dependent upon the objectives of that imaging.

4 DISCUSSION: FUTURE OF EVAR SURVEILLANCE RESEARCH AND CLINICAL PRACTICE

This thesis has presented novel data regarding the indication, incidence and distribution of secondary interventions following Endovascular aneurysm repair (EVAR). It has demonstrated that with a robust administrative process it is possible to achieve excellent compliance with EVAR surveillance. It shows that the factors associated with compliance are often co-linear and display potential confounding, and that relatively few of these factors are independently associated with compliance. It demonstrated that it is possible to accurately predict future secondary interventions based on the data available on a single routine Colour Duplex Ultrasound Scan (CDUS) performed for EVAR surveillance. It has also shown that it is likely to be possible to instigate required secondary interventions while collecting fewer observations on CDUS and Abdominal radiography (AXR). Contrast Enhanced Ultrasound (CEUS) has been shown to have poorer diagnostic abilities than previously stated and likely has a very limited role in endoleak diagnosis in future EVAR surveillance programmes. The comparative data used from time-resolved Computer Tomography Angiography (tCTA) however offers exciting prospects for enhancing and improving the acquisition protocols for ‘standard’ Computer Tomography Angiography CTA.

This chapter discusses the methodology used to obtain these data and suggested areas for improvement and potential benefits of further research and how to maintain the clinical applicability of EVAR research into the future.

4.1 Background

The overall aim of this thesis was to produce an evidence base to facilitate the creation of an efficient, evidence based EVAR surveillance regimen. Initial surveillance regimens were empirically designed and remained remarkably similar to those described by Parodi et al. in 1991, despite surveillances objective being to identify complications and Parodi et al. objective being to prove the efficacy of endovascular aneurysm repair (EVAR).[39] These early generations of EVAR surveillance regimens are still recommended by some stent-graft manufactures, including up to 4 visits for imaging in the first year.[84] Incrementally imaging intensity in the first year after EVAR steadily decreased in clinical practice and research studies.[93] CDUS is also used more frequently and CTA less frequently due to concerns over radiation exposure, financial cost, and potentially nephrotoxic contrast agents.[78] Finally a binary method to stratify EVAR surveillance by patient risk level has just been adopted into European clinical guidance.[53] These incremental changes to the original empirical design have occurred slowly and primarily made based on retrospective cohort studies, with or without external validation.[78]

The cost associated with surveillance and secondary interventions are a significant portion of the overall cost of effective EVAR treatment.[36] While the need for secondary interventions is a limitation of the technology and its applicability, the cost associated with surveillance has long been identified as a target for improvement. Recent assessment of imaging techniques have shown a predominately CDUS and Abdominal Radiography (AXR) based surveillance regimen was highly likely to be more cost effective than a CTA and AXR regimen.[128] A de novo design for an efficient surveillance regimen to detect EVAR complications (or impending complications) seen in current clinical practice would likely have a very different structure to those currently employed. Such a design would also be capable of taking real world factors into consideration such as: compliance and cost effectiveness. To aid the design of an efficient EVAR surveillance regimen the areas requiring better definition were:

- The incidence and indication for secondary interventions and how they vary over time following EVAR
- It is possible to accurately predict the risk of subsequent secondary intervention using current surveillance findings, at any time in EVAR surveillance.

- The importance of each finding recorded during CDUS amd AXR and assess the potential for reducing the number collected without reducing association with subsequent secondary interventions.
- Investigate CEUSs endoleak diagnostic values, to define the evidence base for its role.
- Quantify compliance over time following EVAR and association to other factors, so offering targets to potentially improve compliance.

4.2 Epidemiology of EVAR Complications

Prior to this work the various modes and methods of EVAR stent-graft failure were well described in the literature, section 1.3.2 (page 9), however the timing of these differing complications was not well described. The number of individual patients undergoing secondary intervention was also well described by multiple studies which report "freedom from secondary intervention",[44] this analysis unfortunately masks all information about subsequent interventions in those patients which are essential for effective surveillance regimen design. Finally the global incidence of secondary interventions across all follow-up is reported in some studies, notably the UK EVAR trial 1,[36] but defining secondary intervention rates at differing times can inform differing imaging techniques optimised for differing complications at different times after EVAR.

The use of secondary interventions as a surrogate of EVAR complications is well rehearsed in EVAR studies,[44] Secondary interventions do not offer a total picture of EVAR complications because: some individuals who have a complication will decline a secondary intervention; some will be unsuitable for the required intervention; and unfortunately some will die of (or with) the complication before a secondary intervention is undertaken. The main advantage of using the surrogate of secondary interventions is that it is a definitive standard (they either occurred or did not) and it also represents the reality of current clinical practice, which is why it was selected for this study. These data can inform surveillance regimen design to clinical practice as it is today, i.e. it is inefficient to use data to create a regimen that discovers complications that are not intervened upon.

A proportion of the complications that were not intervened upon will have been detected and reported in the imaging available in these data, with the addition of a complete set of "cause of death" data, from the office of national statistics (ONS), this would give a fuller picture of the complication rates of EVAR. An even more

exhaustive method would to have been to obtain all clinical coding data from national hospital episode statistics (HES) data, which is methodological and ethically more complex. ONS cause of death data and HES coding data are acknowledged to have an error rate in them, systemic review of coding data has shown a median error rate of 20% for primary diagnosis accuracy and 16% for procedure coding.[129] This is normally compensated for by using large datasets that are not currently available in EVAR surveillance research. ONS cause of death data would have similar, less pronounced concerns. This technique would however have the benefit of identifying, after appropriate validation, EVAR complications that occurred outside the performing centre- which is a significant limitation of these presented data. It would also highlight those that have died from an aneurysm related cause. Ethically, written informed consent would be required to obtain such HES and ONS data as much of it may not directly relate to care associated with the individuals EVAR – as such this is probably unrealistic to obtain consent in a sufficiently large enough proportion of patients for meaningful research and certainly not in a single centre study.

The 75% of secondary interventions that occurred prior to any symptoms occurring (section 2.4.2.1, page 55) suggest it may have been possible to define complications based primarily on findings within the imaging data that was available in these studies. While some complications in EVAR having defined criteria- such as migration (section 1.3.2.2, page 11), others are not well defined- such as limb stenosis (section 1.3.2.3, page 12) and therefore definition of a complication becomes an issue that requires resolution prior to such analysis being performed. This effectively needs to be investigated in two constituent parts, the risk that a finding gives of a complication occurring and also the effectiveness that secondary interventions then have at preventing that complication occurring. The effectiveness of secondary interventions is not addressed in this work as these data, from this study, did not feature sufficient numbers of any individual secondary intervention to warrant investigation in this manner but a large multicentre data set may manage to collect such data.

Thinking of future surveillance practice, it would ultimately be useful to know about EVAR complications regardless of secondary intervention both to allow targeted improvements in stent-graft design by manufacturers but would also allow separation of stent-graft complications (present/absent) from patient physiology (suitable/unsuitable) within the considerations of surveillance i.e. some patients in EVAR surveillance either shortly after EVAR or decades later becomes unsuitable for certain secondary

interventions. This separation would allow the interplay between non-aneurysm related patient physiological limitations and aneurysm/stent-graft related limitations to be discerned therefore allowing further improvements in efficiency in surveillance regimen design. This would help account for changes in practice in EVAR implantation as well as changes in patient physiology over time e.g. increasing life expectancy and fitness at similar ages. It could mean that a physiologically unfit patient may having increased intervals of surveillance as only complications that they could have treated by secondary intervention may be rarer than those that would not be intervened upon, equally the data collected on those surveillance visits may inform the risk of complication for a more physiological fit patient that had a similar aneurysm morphology and stent-graft. Liverpool Vascular and Endovascular Service (LiVES) already undertakes this differentiation at a high binary threshold in that, patients are discharged if unsuitable for any secondary intervention. In the future an assessment of functional status at each surveillance visit, and assessing how this correlates to suitability for various secondary interventions may offer a simple manner to graduate this process and would be a simple addition to each surveillance imaging visit.

4.3 Compliance with EVAR surveillance

Compliance with the entirety of EVAR surveillance regimens is undoubtedly poor, as reported in the literature.[70 71 88] The maximum level of compliance that is achievable, how to achieve such levels and what level of compliance is actually necessary to maintain outcomes remains poorly investigated, reported and understood. The excellent levels of compliance seen in LiVES till 10 years after EVAR is encouraging and unlikely to be significantly improved upon in the clinical practice, although this level is partly due to the definition of compliance used (imaging in the last 18 months),[88] and that actively discharged patients were excluded means direct comparisons are difficult – literature based on administrative datasets are not able to identify actively discharged patients. The cross-sectional nature of the study meant that it was not possible to perform similar cohort analysis such as those in the literature, such analysis would be given remarkably useful to benchmark these data to those already published. It could have been explored for the subgroup of patients who had undergone their EVAR within the time frame of the study, unfortunately the study contained a significant number of patients who had their EVAR as part of local mentoring schemes with other units and as such the data would have been very skewed toward early review prior to surveillance

being transferred to their local unit. The fact that at a similar timeframe LiVES demonstrated an 88% compliance rate with surveillance within the UK EVAR-screen study does demonstrate that retrospective and administrative data sets are likely to be reporting marginally lower compliance compared to the methodology used in this work. The study suggests that simply measuring compliance at the end of the observational period is likley to underestimate overall compliance with the regimen as a whole, binarily measuring compliance with the entire surveillance protocol is similarly unlikely to give an accurate assessment of efficacy.

The EVAR-screen study, showed an association between increased distance to surveillance imaging and non-compliance,[88] however these data presented here demonstrated the reverse association. This may well be the result of greater compliance among tertiary referral patients than those referred locally and/or that the majority of local patients lived within the tolerable travel distances as LiVES has a relatively geographically compact referral area. Further interrogation of these data regarding these factors may offer information to help target intervention research. This in addition to the decreased compliance seen in patients who underwent operations more recently suggests that, anecdotally, the role of pre-operative counselling (which is likely to be more extensive in complex tertiary referrals and in patients operated on nearer the introduction of EVAR). This hypothesis is re-inforced by the fact that patients who have undergone secondary intervention (thereby having understood the purpose of surveillance) are more compliant. Therefore potentially more geographically disperse centres could undertake a relatively simple 4 arm RCT, were standard vs enhanced pre-operative counselling and centralised vs localised surveillance imaging were compared, such a study with surveillance compliance as the outcome would be a relatively simple design and allow the interaction and co-linearity between these factors to be discerned, ethically it would not be contentious and may offer a definitive answer to optimising patient dependent factors for EVAR surveillance.

LiVES surveillance regimen (imaging technique and intensity) is largely consistent with that of other centres in the UK EVAR-screen study, so it seems unlikely that this explains the higher levels of compliance observed in LiVES. The administrative processes that are used to achieve compliance (with the surveillance regimen) are not described between differing centres and is likely to play a significant role in the levels of compliance observed. The ‘fail safe’ method of an independent database, out with routine clinical systems, is the backbone of this system that prevents the possibility of

patients being passively lost to follow-up. This supported by administrative staff time dedicated to ensuring EVAR surveillance imaging is requested and completed in a timely manner, and to chase missed appointments and record patient outcomes are what is locally attributed to the success of LiVES EVAR surveillance programme. Implementing such a programme in a centre with poor compliance would be the ideal method to test its' relative effectiveness beyond what can be achieved using routine systems and clinician time, which is anecdotally what is used in the majority of UK centres. This would allow the comparison of pre and post implementation compliance rates and interestingly would also allow the rates of secondary interventions to be measured (giving an indication if increased compliance does increase secondary interventions, as would seem logical).

Such prospectively maintained databases will be essential if surveillance compliance is to be accurately measured and monitored in the era of personalised surveillance regimens, retrospective and administrative dataset studies will become difficult to perform as results will be so dependent on correct assessment of a patients expected next surveillance visit. There will be, as there is now, a risk that "compliance" only infers that the patient did not attend for surveillance, while the administrative process of correctly instigating and inviting the patient for surveillance imaging is equally imperative. Alternatively assessment of the percentage compliance in a centre and the number of patients presenting for secondary interventions with symptoms or as an emergency may offer alternative surrogate markers to monitor surveillance effectiveness rather than true compliance.

4.4 Surveillance Efficiency – Risk Stratification

The secondary intervention risk prediction model created from these data is a significant divergence from previous work on risk stratification in the arena of EVAR surveillance. Previous work has simply tried to divide patients into high/low risk groups, the most successful, validated by Baderkhan et al.,[92] is now recommended in European guidance.[53] This is based purely on 'aneurysm related' secondary interventions - which runs contrary to patient fears / preferences stated in the IMPROVE trail and the prevalence of stent-graft limb secondary interventions seen in these data, section 2.4.2.2 (page 57).[61] As such it assess the length of seal zones proximally and distally that have a protective effect against aneurysm expansion and subsequent effacement by having a longer zone that can undergo effacement before graft-related endoleaks occur. Within

their model this is assessed on the first post-operative CTA to risk stratify the patient for 5 years, however the theory of protective effect from long satisfactory seal zones should be true at any point in post-operative surveillance. It would have been interesting to include an analysis of the seal zone lengths in the CT's performed in these data, as these both would have been an additional validation of Baderkhan et al.'s model, allowed assessment of risk stratification regarding stent-graft limb secondary interventions and likely added additional precision to the risk predictions given in our model throughout surveillance. Unfortunately this was not possible under the ethical approval given but may have improved the accuracy of predictions. The creation of an accurate model is only part of the process of using risk stratification in clinical practice, it must also be validated in clinical use to confirm that when used prospectively in a clinical setting that it does in fact reach the same accuracy and implementation dose not lead to excessive patient or clinician anxiety resulting in a slow regression to previous surveillance regimens due to familiarity.

The fact that the stratification is repeated on each surveillance visit within the model presented in this thesis is a huge benefit and reduces the effect that extrinsic factors can have on the prediction's accuracy – thereby improving accuracy. This repeated scoring on each patient means that smaller patient cohorts are required to create and validate the models' predictions, thereby increasing the accuracy. The greater the accuracy of predictions the longer the intervals between surveillance can be extended in patients with a low risk of prediction error. In the future adding the previously discussed functional status (section 4.4, page 169), may improve prediction accuracy further, the addition of a continuous measure related to the risk of limb stenosis may also make a reasonable addition. If a dataset large enough could be created then addition of all data points and there interplay is likely to influence prediction accuracy, at a certain stage this would no longer lend itself to traditional statistical modelling and may instead be better performed by machine learning, likely in the form of a neural network. A neural network by definition would allow the complex interplay and co-linearity between a large dataset. It is not currently available and is unlikely to have sufficient data accuracy or a sufficient volume of data without a nationwide common dataset that is collected in prospective routine practice. This potentially fits well with the hypothesis regarding having a robust administrative process to improve compliance and such a database combined with standardised administrative process could produce such a dataset.

A modest increase in volume of these current data would have allowed the maximum possible accuracy of the model to have been predicted, such an analysis would be undertaken by using increasingly large proportions of the dataset and it would be possible to plot the Receiver Operator Characteristics (ROC) for that proportion of the data set. As the proportion used increased the AUC should improve, but each increase in proportion will yield a lower increase in AUC until a plateau is reached. With a larger dataset it would have been possible to project these ROC improvements and determine what volume of data is required to achieve a ROC near the plateau. Unfortunately the number of secondary interventions in the LiVES data set meant that it was not possible to attempt this as reducing the proportion of data used would mean some time-frames of the model would have no events to produce the model.

4.5 Surveillance Efficiency – Optimising imaging

Most EVAR imaging publications simply refer to the overarching technology used to acquire EVAR images and fail to adequately describe the; acquisition protocol, definition of findings and reporting standards / template used. Consequently, validation studies are difficult to perform, and diagnostic results are difficult to replicate in clinical practice. Endoleak, the most investigated diagnosis in EVAR imaging studies, is a good example: to make a complete endoleak diagnosis the endoleak must be both detected and correctly characterised, most studies do not offer sufficient detail to confirm that the diagnostic values reported are for a full diagnosis or simply the detection of that endoleak. In addition, the significant number of unblinded studies are likely to have suffered from confirmatory bias, between imaging modalities, regarding endoleak characterisation. The comparison of contrast enhanced ultrasound scans (CEUS) and time-resolved CTA (tCTA) in these data address the above issues and report a markedly different sensitivity to diagnose a graft-related endoleak than the literature, 0.56 reported vs ~0.95 in the literature.[73] Given the unexpectedly low sensitivity the study was under powered and terminated early meaning that there is a wide confidence interval, however validation studies could easily be performed given the standard of the reporting within the study. It would suggest that CEUS has little to add to CDUS in the sub-population going on to CT scan due to concerns during CDUS EVAR surveillance (the recruitment population). As such the role of CEUS should likely to be limited to patient who have contra-indications to CT scanning or cases of persistent diagnostic uncertainty in which additional imaging modalities are required. The addition of a 3D

CEUS imaging arm would have been an interesting addition to the study to discern what it adds to the diagnostic values of CEUS, although it is a static 3D picture that this technology can currently provide rather than 4D (time being the 4th dimension) imaging that tCTA is providing. The cost of 3D CEUS prohibited its addition to this study and currently is likely also a barrier to use in clinical practice. The calculation of intra- and inter- observer variability values of the CEUS and tCTA findings would have been a valuable addition to the study, adding additional validity, but previous tCTA studies have shown high level of agreement in reporting and CEUS has been investigated and they require additional staff, patient and resource time.[122] The curtailment of the study prevented more detailed analysis of endoleak filling patterns on tCTA which potentially could have allowed exploration of the optimum timing of CTA phases for detecting different classes of endoleaks. There is now likely to be sufficient tCTAs within published studies that if combined into a single cohort they could be prospectively re-analysed blindly by multiple radiologists in constituent parts to allow a focused logical process to develop such a protocol. This would likely involve a series of blinded double reporting of contrast filling patterns to allow filling patterns to be robustly reported and validity of such measurements to be confirmed, then optimum timing of phases defined. Once these timings have been defined then a repeat process of only these selected phases being made available for blinding reporting by two radiologist and different times (who had not previously seen those examinations) could be undertaken to confirm inter- and intra- observer variability and diagnostic values to be defined. This would be a laborious process but would allow optimum CTA timings to be definitively defined. The inability in this study to use the CTA reports due to diverse reporting does demonstrate a need for a minimum reporting set / standard.

Colour Duplex Ultrasound Scan (CDUS) and abdominal X-ray (AXR) remain the most utilised EVAR surveillance imaging technique in the UK. AXR has a standardised acquisition protocol, the Liverpool-Perth protocol,[74] however CDUS does not currently have such a protocol within the scientific literature. LiVES has a standard operating procedure (appendix 1, page 188) which was perspicaciously designed based on best knowledge and expert opinion, this allowed analysis of the constituent parts for association with subsequent secondary intervention. The analysis of the associations between differing findings on CDUS and broad categories of secondary interventions is the first attempt, to our knowledge, to methodically / scientifically derive the findings required to discern if a secondary intervention is required. Such moves to rationalise

findings investigated is a route to improve the efficiency of CDUS imaging within EVAR surveillance. It was limited by the quantity of data available and therefore findings that trigger rarer interventions were more likely to be excluded, this could be overcome by larger datasets. These data particularly highlight the need for an efficient defined measurement to identify patients who may benefit from secondary intervention to prevent symptomatic stent-graft limb stenosis or occlusion. The definition of significance within such a finding could be identified relatively simply with multiple measures taken on a single CDUS in a group of patients followed by a period of follow-up in which they were monitored for limb occlusion or secondary intervention. Once the optimum finding and cut off have been defined its collection should be emphasised in early and late surveillance following EVAR given that the early and late prominent incidence of these findings following EVAR (section 2.4.2.2, page 57)

The analysis demonstrating increased association of secondary interventions in the 6 months following EVAR surveillance imaging is perhaps the strongest demonstration in the literature that EVAR surveillance does indeed precipitate secondary interventions directly. The return to slow baseline relative risk demonstrates that there is a slow rate of secondary interventions that occur regardless of surveillance imaging, unfortunately these are insufficient in number to tease out the causation of these baseline interventions. If these baseline interventions were predominantly symptomatic or the result of incidental findings on other forms of imaging this would be an interesting observation and add weight to the hypothesis that effective EVAR surveillance leads to a low rate of symptomatic presentations. A clinical study to randomly compare no surveillance with surveillance imaging would unlikely be ethical and unlikely to recruit adequately- due to lack of equipoise in clinicians' and patients attitudes, however a study of planned surveillance imaging or imaging delayed for 6 months for those in routine EVAR surveillance may be less controversial, if this detected different prevalence in planned and unplanned secondary interventions between the groups it would demonstrate surveillance having its intended effect, although would not prove its efficacy. Even such a study, that delayed surveillance, would be ethically challenging as it potentially puts those in the delayed surveillance group at risk of preventable harm, but the cost of EVAR surveillance should be justified and without a study demonstrating definitively that it does precipitate secondary interventions intended to prevent harm it may struggle to justify the costs associated with it.

These data show an apparent progressive relationship between minor then major migration reported on AXR (compared to no migration) and subsequent aneurysm related secondary intervention. While only major migration showed statistically different intervention rates this may simply be related to the sensitivity of detection. The multiple possible geometric confounders caused by comparison of single or two plane imaging used in EVAR surveillance AXR may simply be to complex for unassisted human interpretation to achieve better granularity/definition than this. Computer aided alignment and adjustment may well allow for better granularity/detection of migration and therefore more direct correlation between AXR and secondary intervention. This is appealing as CDUS based surveillance regimens are lower cost than CTA regimens but miss out on stent-graft structure and anatomical relationships, unless combined with AXR.

Effacement correlates with migration, detection of the surrogate of effacement (proximal dilation) seen on AXR is more difficult than migration due to the smaller changes seen in terms of millimetres, however changes in form and geometry of the proximal stent are often also seen and were the isolated finding that precipitated aneurysm related secondary interventions in some patients. As such shape (effacement) and position (migration) of the stent graft should be the focus of any attempts to automate the analysis of AXR's. The main benefits I suspect would arise from the superior abilities from automated alignment of serial AXRs across EVAR surveillance, compared to manual visual comparison.

4.6 Conclusion

This thesis demonstrates:

- An ongoing need for EVAR surveillance with secondary interventions remaining prevalent in a contemporary surveillance programme with the majority being undertaken electively in asymptomatic patients.
- It establishes the indication and incidence of secondary interventions changes, over the post-operative course, following EVAR
- It demonstrates it is possible to accurately and reliably predict the risk of secondary interventions at multiple time points.
- It has established there is co-linearity and likely confounding between variables associated with poor EVAR surveillance compliance, but that good rates of compliance are possible.

- It has called into question the endoleak diagnostic accuracy of CEUS reported in the literature

These data help progress the area of research in the area of surveillance following EVAR for the treatment of infra-renal AAA, they however do not offer sufficient evidence in themselves to unify the diverse range of surveillance regimens and imaging techniques / protocols used in the UK, they instead highlight a need and offer a potential pathway to such a unification of differing techniques through further targeted research.

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6 APPENDICES

1. Liverpool Vascular and Endovascular Service: Colour Duplex Ultrasound Scan in Endovascular Aneurysm Repair Surveillance – Standard Operating Procedure

Staff

To be conducted by a Clinical Vascular Scientist

Location

Vascular Laboratory, Vascular Clinic, Royal Liverpool Hospital

Measurements

PSV in cm/s
Diameter, length in mm

Abbreviations

LS – Longitudinal Section
TS – Transverse Section
AP – Antero Posterior
ML – Medial Lateral

Patient Positioning

Please refer to Institute of Physics and Engineering in Medicine Vascular Laboratory Practice [ISBN 0903613051]

Probe

Abdominal 2-5MHz curved Array

Procedure

Using grey scale imaging the; aneurysm neck (when possible), iliac seal zone and maximum aneurysm dimensions are measured in LS and TS. The maximum TS (both AP and ML) dimensions are recorded for the aneurysm and iliac vessels and maximum LS dimensions for the aneurysm neck.

Notes are to be made of the echogenicity of thrombus within the aneurysm sac i.e. echo lucent areas or homogenous.

The native iliac system iliac artery and common femoral arteries are imaged using colour flow imaging and spectral Doppler, making note of the waveform characteristics

and velocity at this point. Any arterial disease of the iliac segment distal to the respective limb of the endograft is also to be noted, assessed and reported as per arterial duplex protocol.

The Endograft is now interrogated using colour and spectral Doppler to ascertain patency and flow heamodynamics of the main body of the endograft as well as both limbs. Any abnormalities in these parameters are to be reported. Velocity changes are to be assessed as per arterial duplex protocol and the cause reported.

The aneurysm is to be assessed using colour Doppler to identify arterial blood flow outside of the endograft but within the aneurysm sac (endoleak). If flow is identified it is confirmed with spectral Doppler and its source identified i.e. IMA, Lumbar, proximal/distal seal zone and the appropriate type of endoleak reported.

Seromas and lymphoceles can be noted at the incision site in the groin. Size and location are to be noted.

2. R Code For Data Processing And Analysis Of A Colour Duplex Ultrasound Scan And Plain Abdominal X-ray Surveillance Regimen

A copy of this code is also available on the accompanying CD in the pocket attached to the inside back cover, along with the saved RData files created by it (to allow exact replication of the results presented).

CD\database\analysis.R

CD\database\midata.RData

CD\database\data.RData

CD\database\model.RData

```
# Code Created by Iain N Roy, Institute of Ageing & Chronic Disease,
University of Liverpool - Except were indicated
# Contact via iainroy@liverpool.ac.uk
# Code to process data for
# Study Title: "Liverpool Vascular & Endovascular Service:
Endovascular Aneurysm Repair Surveillance Data Analysis"
# Study Ethical approval: NHS REC reference: 17/NS/0088

# Code created in R Studio v1.1.463 using R version 3.5.2
# The study data (patient_level_data.csv, secondary_interventions.csv,
all_scans.csv) is assumed to be in the working directory

# Loading Required Packages
install.packages(c("tidyverse","survival","scales","survminer","Cairo"
,"Epitools", "caret","MASS", "corr", "mice", "survivalROC","pROC"))
library(tidyverse)
library(survival)
library(scales)
library(survminer)
library(Cairo)
library(epitools)
library(caret)
library(MASS)
library(corrplot)
library(mice)
library(survivalROC)
library(pROC)
### Load & Catagorise Data
patient_data <- read.csv("patient_level_data.csv", header = TRUE,
col.names = c("Database ID","Calander Year of Operation","Age at
Operation in Years","Gender","Max Pre-op Diameter in mm",   "Max Pre-
op Iliac Diameter in mm",     "EVAR Device Type",     "EVAR Device
Supplier",  "Distance to Surveillance Centre in km",  "Time from
Operation to Death in Years", "Time from Operation to No Follow-Up in
Years",     "Reason No Follow-Up", "Time from operation to Start of
Observational period in Years"))
secondary_interventions <- read.csv("secondary_interventions.csv",
header = TRUE, col.names = c("Database ID","Time since Operation in
```

```
Years","Emergency","Treating","Intervention", "side","Patient
Symptomatic","Detected on Surveillance","Comments","SI_Type"))
all_scans <- read.csv("all_scans.csv", header =TRUE, col.names =
c("Database ID", "Time since Operation in Years","Examination","Exam
Name","Surveillance Imaging", "Primary EVAR Procedure","Potential
Secondary Intervention", "AXR Baseline","AXR Compared To AXR Years
After Op","AXR Abnormal", "AXR Migration", "AXR Left Limb Kink","AXR
Right Limb Kink","AXR Structural Failure","AXR Complication type","AXR
Non EVAR Finding",      "AXR Effacement","CDUS EVAR
Surveillance","CDUS Diagnostic","CDUS Diagnostic Comments","CDUS AAA
size in mm","CDUS Right CIA in mm","CDUS Left CIA in mm","CDUS
Endoleak Present","CDUS Endoleak Type", "CDUS Endoleak Text","CDUS
Mixed Thrombose in AAA", "CDUS Limb Complication","CDUS Limb
Effected", "CDUS Limb Complication Type", "CDUS Comments"))

###Global Manipulation of data###
patient_data$old <-
ifelse(0<=patient_data$Time.from.operation.to.Start.of.Observational.p
eriod.in.Years, TRUE, FALSE)
#patient_data$fu_years <-
patient_data$Time.from.operation.to.Start.of.Observational.period.in.Y
ears+7
patient_data$start <-
ifelse(0>patient_data$Time.from.operation.to.Start.of.Observational.pe
riod.in.Years, 0,
patient_data$Time.from.operation.to.Start.of.Observational.period.in.Y
ears)
patient_data$died <-
ifelse(is.na(patient_data$Time.from.Operation.to.Death.in.Years),FALSE
,TRUE)
patient_data$years<-
ifelse(is.na(patient_data$Time.from.Operation.to.Death.in.Years),(pati
ent_data$Time.from.operation.to.Start.of.Observational.period.in.Years
+ 7), patient_data$Time.from.Operation.to.Death.in.Years)
patient_data$ends <-
ifelse(is.na(patient_data$Time.from.Operation.to.No.Follow.Up.in.Years
),
patient_data$years,patient_data$Time.from.Operation.to.No.Follow.Up.in
.Years)

###Patient level Demographics###
print(summary (patient_data))
print(summary (patient_data$EVAR.Device.Supplier))
print(summary(patient_data$EVAR.Device.Type))
#Create histogram of number of cases per year
Cairo(file="time_of_evar.png", type="png",units="mm", width= 140,
height = 100, dpi=600, ponitsize="1")
ggplot(data=patient_data, aes(x=Calander.Year.of.Operation,
fill=patient_data$old))+
  geom_histogram(binwidth = 1)+
  xlab("Calander Year") +
  ylab("Number of Patients")+
  scale_x_continuous(breaks =seq.int(1996,2014,2))+
  scale_fill_discrete(name="EVAR",
                      breaks=c("FALSE", "TRUE"),
                      labels=c("EVAR during observation Period    ",
"EVAR before observation Period"))+
  theme(legend.title=element_blank(), legend.position = "bottom")
dev.off()
#Patient level all cause survival curve
fit <- survfit(Surv(patient_data$years,patient_data$died)~1, data
=patient_data)
```

```
Cairo(file="all_cause_survival.png", type="png",units="mm", width=
140, height=100, dpi=600, ponitsize="1")
ggsurvplot(fit,risk.table = TRUE, pval = FALSE, conf.int = TRUE,
break.time.by = 2, censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.3, xlab="Years", ylab="All Cause Survival", surv.scale="percent",
legend.title = " ", legend = "none", xlim = c(0, 18))
dev.off()
rm(fit)
#create data for Secondary intervention KM of EVAR during
observational peroid
secondary_interventions <- secondary_interventions %>%
arrange(Time.since.Operation.in.Years)
si <- left_join(patient_data, secondary_interventions,
by="Database.ID", no.dups = FALSE)
si <- si %>% arrange(Time.since.Operation.in.Years)
si <- distinct(si, Database.ID, .keep_all = TRUE)
si$si <- ifelse(is.na(si$Time.since.Operation.in.Years), FALSE, TRUE)
si$siTIME <- ifelse(is.na(si$Time.since.Operation.in.Years), si$years,
si$Time.since.Operation.in.Years)
si <- subset(si, old == FALSE)
#Create KM of secondary intervention
fit <- survfit(Surv(siTIME,si)~1, data =si)
Cairo(file="freedom_si.png", type="png",units="mm", width= 140,
height=100, dpi=600, ponitsize="1")
ggsurvplot(fit,risk.table = TRUE, pval = FALSE, conf.int = TRUE,
break.time.by = 1, censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.3, xlab="Years", ylab="Freedom from \n Secondary Intervention",
surv.scale="percent", legend.title = " ", legend = "none", xlim = c(0,
7), ylim= c(0.5,1))
dev.off()
rm(fit, si)

###Secondary Intervention analysis###
#Data work
si_analysis <- left_join(secondary_interventions, patient_data,
by="Database.ID", no.dups = FALSE)
si_analysis$in_observational_peroid <-
ifelse(si_analysis$Time.since.Operation.in.Years>=si_analysis$start,if
else(si_analysis$Time.since.Operation.in.Years<=si_analysis$ends,TRUE,
FALSE),FALSE)
si_analysis$in_observational_peroid <- ifelse(si_analysis$Intervention
== "Aneurysm Related Death", FALSE,
si_analysis$in_observational_peroid)
si_analysis <- subset(si_analysis, si_analysis$in_observational_peroid
== TRUE)

#Descriptive statistics for Secondary Interventions#
print(count(si_analysis))##number of secondary interventions
length(unique(si_analysis$Database.ID)) ##number of unique individuals
those secondary interventions they are in
summary(si_analysis) # general demographics of secondary interventions
summary(subset(si_analysis$Treating,si_analysis$SI_Type=="Aneurysm"))
##indication for secondary intervention in aneurysm related cases
summary(subset(si_analysis$Treating,si_analysis$SI_Type=="Flow"))
##indication for secondary intervention in flow related cases
summary(si_analysis$Intervention) #interventions undertaken


#Secondary Intervention Incidence Calculation#
#Total at risk period from $start - $ends#
#calculate portion of year at risk
```

```
span=1
x=1       # time incidence measured over- 1=1year 0.5=6months
y_vals<- c((x*100):1500)/100 #time points indicdence measure too
incidence_graph <- as.data.frame(matrix(ncol = 3, nrow =
length(y_vals)))

for(j in seq(y_vals)){
  y= y_vals[j]
  z=y-x
  incidence <- left_join(patient_data, si_analysis, by="Database.ID",
no.dups = FALSE)
  incidence$Time.since.Operation.in.Years <- ifelse
(incidence$Time.since.Operation.in.Years<z,NA,ifelse(incidence$Time.si
nce.Operation.in.Years>y,NA,incidence$Time.since.Operation.in.Years))
  incidence <- incidence %>% arrange(Time.since.Operation.in.Years)
  incidence <- distinct(incidence, Database.ID, .keep_all = TRUE)
  incidence$time_at_risk <- ifelse(
    (ifelse(incidence$ends.x<y,incidence$ends.x,y)-
ifelse(z>incidence$start.x,z,incidence$start.x))<0,
    0,
    (ifelse(incidence$ends.x<y,incidence$ends.x-z, y-z)))

  incidence_graph[j,1:3] <-
c(y,sum(!is.na(incidence$Time.since.Operation.in.Years)),
sum(incidence$time_at_risk))
  rm(j)
}
colnames(incidence_graph) <- c("year","events","years_at_risk")

#table patients years at risk
print(incidence_graph [c(1,seq(101,1401, by=100)),c(1,3)])

#calculate frequency of events
incidence_graph$frequency <- (incidence_graph$events
/incidence_graph$`years_at_risk`)*1000
# produce the best fit loess model weighted to number of years at risk
model <- loess(frequency ~sqrt(year), data=incidence_graph, weights =
years_at_risk, span = span)
smoothed_line <- data.frame(frequency=predict(model, incidence_graph),
year=incidence_graph$year)

Cairo(file="frequency_si.png", type="png",units="mm", width= 140,
height = 86.5, dpi=600, ponitsize="1")
ggplot(incidence_graph,aes(year,frequency))+
  geom_line()+
  scale_x_continuous(breaks = seq(1, 15, by = 1))+
  scale_y_continuous(breaks = seq(0, 130, by = 25))+
  xlab("Years Since Patient Underwent EVAR")+
  ylab("Incidence of Secondary Intervention\nin previous 12 months\n
per 1000 patient years at risk")+
  geom_line(color='red',size=1,data = smoothed_line, aes(x=year,
y=frequency))
dev.off()

lines<-data.frame(smoothed_line,"All")
colnames(lines) <- c("Frequency","Year","Group")


#Graph of Aneursym preservation secondary interventions
incidence_graph <- as.data.frame(matrix(ncol = 3, nrow =
length(y_vals)))
for(j in seq(y_vals)){
  y= y_vals[j]
```

```
  z=y-x
  incidence <- left_join(patient_data, si_analysis, by="Database.ID",
no.dups = FALSE)
  incidence$Time.since.Operation.in.Years <- ifelse
(str_detect(incidence$SI_Type,"Aneurysm"),incidence$Time.since.Operati
on.in.Years, NA)
  incidence$Time.since.Operation.in.Years <- ifelse
(incidence$Time.since.Operation.in.Years<z,NA,ifelse(incidence$Time.si
nce.Operation.in.Years>y,NA,incidence$Time.since.Operation.in.Years))
  incidence <- incidence %>% arrange(Time.since.Operation.in.Years)
  incidence <- distinct(incidence, Database.ID, .keep_all = TRUE)
  incidence$time_at_risk <- ifelse(
    (ifelse(incidence$ends.x<y,incidence$ends.x,y)-
ifelse(z>incidence$start.x,z,incidence$start.x))<0,
    0,
    (ifelse(incidence$ends.x<y,incidence$ends.x-z, y-z)))

  incidence_graph[j,1:3] <-
c(y,sum(!is.na(incidence$Time.since.Operation.in.Years)),
sum(incidence$time_at_risk))
  rm(j)
}
colnames(incidence_graph) <- c("year","events","years_at_risk")
# plot raw frequency of 'Aneurysm' related secondary interventions per
1000 patient risk years
incidence_graph$frequency <- (incidence_graph$events
/incidence_graph$`years_at_risk`)*1000
model <- loess(frequency ~ sqrt(year), data=incidence_graph, weights =
years_at_risk, span = span)
smoothed_line <- data.frame(frequency=predict(model, incidence_graph),
year=incidence_graph$year)
# plot raw frequency of 'Aneurysm' related secondary interventions per
1000 patient risk years
Cairo(file="frequency_aneurysm_si.png", type="png",units="mm", width=
140, height = 86.5, dpi=600, ponitsize="1")
ggplot(incidence_graph,aes(year,frequency))+
  geom_line()+
  scale_x_continuous(breaks = seq(1, 15, by = 1))+
  ylim(0, 90)+
  xlab("Years Since Patient Underwent EVAR")+
  ylab("Incidence of 'Aneurysm Related' \n Secondary Intervention in
previous \n 12 months / 1000 patient risk years")+
  geom_line(color='green',size=1,data = smoothed_line, aes(x=year,
y=frequency))
dev.off()
#Store trend line in dataframe 'lines'
all <-data.frame(smoothed_line$frequency,smoothed_line$year,"Aneurysm
Related")
colnames(all) <- c("Frequency","Year","Group")
lines <- rbind(lines,all)
rm(all)
#Create a table of flow related secondary interventions
incidence_graph <- as.data.frame(matrix(ncol = 3, nrow =
length(y_vals)))
for(j in seq(y_vals)){
  y= y_vals[j]
  z=y-x
  incidence <- left_join(patient_data, si_analysis, by="Database.ID",
no.dups = FALSE)
  incidence$Time.since.Operation.in.Years <- ifelse
(str_detect(incidence$SI_Type,"Flow"),incidence$Time.since.Operation.i
n.Years, NA)
```

```
  incidence$Time.since.Operation.in.Years <- ifelse
(incidence$Time.since.Operation.in.Years<z,NA,ifelse(incidence$Time.si
nce.Operation.in.Years>y,NA,incidence$Time.since.Operation.in.Years))
  incidence <- incidence %>% arrange(Time.since.Operation.in.Years)
  incidence <- distinct(incidence, Database.ID, .keep_all = TRUE)
  incidence$time_at_risk <- ifelse(
    (ifelse(incidence$ends.x<y,incidence$ends.x,y)-
ifelse(z>incidence$start.x,z,incidence$start.x))<0,
    0,
    (ifelse(incidence$ends.x<y,incidence$ends.x-z, y-z)))

  incidence_graph[j,1:3] <-
c(y,sum(!is.na(incidence$Time.since.Operation.in.Years)),
sum(incidence$time_at_risk))
  rm(j)
}
colnames(incidence_graph) <- c("year","events","years_at_risk")
# calculate frequency
incidence_graph$frequency <- (incidence_graph$events
/incidence_graph$`years_at_risk`)*1000
# model trend line
model <- loess(frequency ~ sqrt(year), data=incidence_graph, weights =
years_at_risk, span = span)
smoothed_line <- data.frame(frequency=predict(model, incidence_graph),
year=incidence_graph$year)
# plot raw frequency of 'Flow' related secondary interventions per
1000 patient risk years
Cairo(file="frequency_flow_si.png", type="png",units="mm", width= 140,
height = 86.5, dpi=600, ponitsize="1")
ggplot(incidence_graph,aes(year,frequency))+
  geom_line()+
  scale_x_continuous(breaks = seq(1, 15, by = 1))+
  ylim(c(0,90))+
  xlab("Years Since EVAR")+
  ylab("Incidence of 'Flow Related'\n Secondary Intervention in
previous\n 12 months / 1000 patients years")+
  geom_line(color='blue',size=1,data = smoothed_line, aes(x=year,
y=frequency))
dev.off()
#Store Trend Line into dataframe lines
all <-data.frame(smoothed_line$frequency,smoothed_line$year,"Flow
Related")
colnames(all) <- c("Frequency","Year","Group")
lines <- rbind(lines,all)
rm(all)

###Plot all three trend lines
Cairo(file="si_trend_lines.png", type="png",units="mm", width= 140,
height=100, dpi=600, ponitsize="1")
ggplot(lines, aes(Year,Frequency,colour = factor(Group)))+
  geom_line(size=1)+
  xlab("Years Since EVAR")+
  ylab("Incidence in previous 12 months\n/ 1000 patients years")+
  labs(colour="Secondary Interventions:")+
  scale_x_continuous(breaks = seq(1, 15, by = 1))+
  ylim(c(0,90))+
  theme(legend.position="bottom")
dev.off()
###Tidy
rm(incidence_graph,incidence,lines, model, smoothed_line, span, x,
y,z,y_vals)

###Surveillance compliance analysis###
```

```
#data
##all patients with all scans##
compliance <- left_join(patient_data, subset(subset(all_scans,
Surveillance.Imaging==TRUE),Examination!="XABDO"), by="Database.ID",
no.dups = FALSE)
#mark scans that didn't occur in the observational peroid#
compliance$scan_count <- ifelse
(compliance$Time.since.Operation.in.Years>=compliance$start,(ifelse(co
mpliance$Time.since.Operation.in.Years<=compliance$ends,TRUE,FALSE)),F
ALSE)
compliance$scan_count <- ifelse (is.na(compliance$scan_count), FALSE,
compliance$scan_count)

##Graph
x=18/12     # time incidence measured over- 1=1year 0.5=6months
y_vals<- c((x*100):1500)/100 #time points indicdence measure too
compliance_graph1 <- as.data.frame(matrix(ncol = 4, nrow =
length(y_vals)))
for(j in seq(y_vals)){
  y= y_vals[j]
  z=y-x
  compliance <- left_join(patient_data, subset(subset(all_scans,
Surveillance.Imaging==TRUE),Examination!="XABDO"), by="Database.ID",
no.dups = FALSE)
  compliance$at_risk <-
ifelse(compliance$ends>=y,ifelse(compliance$start<=z,TRUE,FALSE),FALSE
)
  compliance <-subset(compliance,at_risk==TRUE)
  compliance$scan_at_risk <-
ifelse(compliance$Time.since.Operation.in.Years<=y,ifelse(compliance$T
ime.since.Operation.in.Years>=z,TRUE,FALSE),FALSE)
  compliance$scan_at_risk <-
ifelse(is.na(compliance$scan_at_risk),FALSE, compliance$scan_at_risk)
  compliance <- compliance %>% arrange(desc(scan_at_risk))
  compliance <- distinct(compliance, Database.ID, .keep_all = TRUE)
  compliance_graph1[j,1:4] <-
c(y,sum(compliance$scan_at_risk),count(compliance),"18 Months")
  rm(j)
}
colnames(compliance_graph1) <- c("year","compliant","number at
risk","deff")
compliance_graph_all <- compliance_graph1
# calculate percentage compliant
compliance_graph_all$percentage <-
(compliance_graph_all$compliant/compliance_graph_all$`number at
risk`)*100
# number at risk
print(compliance_graph_all
[round(compliance_graph_all$year)==compliance_graph_all$year,
c(1,3,4)])

# graph
Cairo(file="surveillance_compliance_time.png", type="png",units="mm",
width= 140, height = 86.5, dpi=600, ponitsize="1")
ggplot(compliance_graph_all, aes(year,percentage, colour =
factor(deff)))+
  geom_line()+
  xlab("Years Since EVAR")+
  ylab("Percetage of patients compliant (%)")+
  labs(colour="Compliant if EVAR surveillance scan in last")+
  theme(legend.position="bottom")+
  scale_x_continuous(breaks = seq(1, 15, by = 1))+
  scale_y_continuous(breaks = seq(0, 100, by = 5))+
```

```
  ylim(c(50,100))
dev.off()

##Patient Factors effecting Compliance##
#Table of patient factors
pf_compliance <-
data.frame(patient_data$Database.ID,patient_data$Calander.Year.of.Oper
ation,patient_data$Age.at.Operation.in.Years,patient_data$Gender,patie
nt_data$Max.Pre.op.Diameter.in.mm,patient_data$Distance.to.Surveillanc
e.Centre.in.km,patient_data$start,patient_data$ends)
colnames(pf_compliance) <- c("Database.ID","year of op", "age at
op","gender", "max pre-op diameter", "distance", "start", "end")
#create a row for each time point for each patient
pf_compliance_alltimes <- pf_compliance
pf_compliance_alltimes$time <- 0
y_vals<- c(1:150)/10 #time points indicdence measure too
for(j in seq(y_vals)){
a <- pf_compliance
a$time <- y_vals[j]
pf_compliance_alltimes <- rbind(pf_compliance_alltimes,a)
}
rm(y_vals)
#remove rows were time points are not in observational peroid
pf_compliance_alltimes$at_risk <- ifelse(pf_compliance_alltimes$time
>= pf_compliance_alltimes$start, ifelse(pf_compliance_alltimes$time <=
pf_compliance_alltimes$end, TRUE,FALSE),FALSE)
pf_compliance <- subset(pf_compliance_alltimes,
pf_compliance_alltimes$at_risk==TRUE)
rm(pf_compliance_alltimes)
#adds secondary interventions to allow calculation of previous
intervention
pf_compliance <- left_join(pf_compliance,secondary_interventions,
by="Database.ID", no.dups = FALSE)
pf_compliance$si_before <-
ifelse(pf_compliance$Time.since.Operation.in.Years <=
pf_compliance$time, TRUE, FALSE)
pf_compliance$si_before <-
ifelse(is.na(pf_compliance$si_before),FALSE,pf_compliance$si_before)
#removes duplicate rows
pf_compliance <- pf_compliance %>% arrange(desc(si_before))
pf_compliance <- distinct(pf_compliance,Database.ID,time, .keep_all =
TRUE)
#add surveillance scans & calculate if compliant
pf_compliance <- left_join (pf_compliance,subset(subset(all_scans,
Surveillance.Imaging==TRUE),Examination!="XABDO"), by="Database.ID",
no.dups = FALSE)
pf_compliance$sur_scan_in_18months <-
ifelse(pf_compliance$Time.since.Operation.in.Years.y-
pf_compliance$time
<=1.5,ifelse(pf_compliance$Time.since.Operation.in.Years.y-
pf_compliance$time > 0, TRUE, FALSE),FALSE)
pf_compliance$sur_scan_in_18months <-
ifelse(is.na(pf_compliance$sur_scan_in_18months),FALSE,pf_compliance$s
ur_scan_in_18months)
#remove duplicates
pf_compliance <- pf_compliance %>% arrange(desc(sur_scan_in_18months))
pf_compliance <- distinct(pf_compliance,Database.ID,time, .keep_all =
TRUE)

##Create final analysis table##
analysis<- pf_compliance [,c("Database.ID","year of op","age at
op","gender","distance","max pre-op
diameter","time","at_risk","si_before","sur_scan_in_18months")]
```

```
analysis$'age at time' <- analysis$`age at op`+analysis$time
###Explore and sort data###
summary(analysis)
ggplot(analysis,aes(x=analysis[,2],group=analysis[,10],
fill=analysis[,10]))+
  geom_density(alpha=0.5)+
  theme(legend.position="bottom")+
  labs(x="Year of Operation", y="Density", fill="Compliant")
# better compliance before 2009 worse after, converted to factor as
year of repair is surrogate for type of operation
analysis$'factor_year_of_op' <- ifelse(analysis$`year of op`<=2009,
"Before 2010","2010 or after")
analysis$'factor_year_of_op' <-
as.factor(analysis$'factor_year_of_op')
ggplot(analysis,aes(x=analysis[,3],group=analysis[,10],
fill=analysis[,10]))+
  geom_density(alpha=0.5)+
  theme(legend.position="bottom")+
  labs(x="Age at Operation", y="Density", fill="Compliant")
# some trend towards better compliance for younger patients

summary(analysis$gender)
## ???????how od you explore factors

ggplot(analysis,aes(x=analysis[,6],group=analysis[,10],
fill=analysis[,10]))+
  geom_density(alpha=0.5)+
  theme(legend.position="bottom")+
  labs(x="AAA Diameter at Operation", y="Density", fill="Compliant")

#no apparent consistent pattern but contains NA's - replace with mean
analysis$`max pre-op diameter`<-ifelse(is.na(analysis$`max pre-op
diameter`),65,analysis$`max pre-op diameter`)
ggplot(analysis,aes(x=analysis[,6],group=analysis[,10],
fill=analysis[,10]))+
  geom_density(alpha=0.5)+
  theme(legend.position="bottom")+
  labs(x="AAA Diameter at Operation (mm)", y="Density",
fill="Compliant")
#no overt pattern

ggplot(analysis,aes(x=analysis[,7],group=analysis[,10],
fill=analysis[,10]))+
  geom_density(alpha=0.5)+
  theme(legend.position="bottom")+
  labs(x="Time Since Operation (Years)", y="Density",
fill="Compliant")
#density of non-compliance higher after 2.5 years
analysis$time_factor <- ifelse(analysis[,7]>=10, "After 10 Years",
"Before 10 years")
analysis$time_factor <- as.factor(analysis$time_factor)
summary(analysis$time_factor)

##
summary(analysis[,9])
##?need to explore above more

ggplot(analysis,aes(x=analysis[,11],group=analysis[,10],
fill=analysis[,10]))+
  geom_density(alpha=0.5)+
  theme(legend.position="bottom")+
  labs(x="Age at time", y="Density", fill="Compliant")
```

```
#Age at time ofscan strongly corrolates to compliance (younger more
compliant)

ggplot(analysis,aes(x=analysis[,5],group=analysis[,10],
fill=analysis[,10]))+
  geom_density(alpha=0.5)+
  theme(legend.position="bottom")+
  labs(x="Distance from Surveillance", y="Density", fill="Compliant")
#distance is vastly skewed - likley effect of teriary practice
majority within 60km
analysis$distance_factor <- ifelse(analysis$distance>=60, "Teriary",
"Local")
analysis$distance_factor <-
ifelse(is.na(analysis$distance_factor),"Teriary",
analysis$distance_factor)
analysis$distance_factor <- as.factor(analysis$distance_factor)
summary(analysis$distance_factor)
#relook at distance for local patients only
local_patients <- subset(analysis,analysis$distance_factor=="Local")
ggplot(local_patients,aes(x=local_patients[,5],group=local_patients[,1
0], fill=local_patients[,10]))+
  geom_density(alpha=0.5)+
  theme(legend.position="bottom")+
  labs(x="Distance from Surveillance", y="Density", fill="Compliant")
#distance still squewed
local_patients <- subset(analysis,analysis$distance_factor=="Local")
local_patients$sqrt_distance<- sqrt(local_patients[,5])
ggplot(local_patients,aes(x=local_patients$sqrt_distance,group=local_p
atients[,10], fill=local_patients[,10]))+
  geom_density(alpha=0.5)+
  theme(legend.position="bottom")+
  labs(x="Distance from Surveillance", y="Density", fill="Compliant")
#apparent better compliance before <~9km, worse between ~9-12km then
equal >~12km
###???should i be changing this to 3 factors??

#corroletion of continious variables (whole cohort)
cor<- cor(analysis[,c(2,3,6,7,11)])
corrplot(cor, method="circle")
#corrolation of continious variables (local patients only)
cor<- cor(local_patients[,c(2,3,5,6,7,11,15)])
corrplot(cor, method="circle")
##??can look at corelation between factos and other variables
=
# Split the data into training and test set
set.seed(123)
training.samples <- analysis$Database.ID %>% createDataPartition(p =
0.8, list = FALSE)
train.data  <- analysis[training.samples,c(2:14)]
test.data <- analysis[-training.samples,c(2:14)]

###added function to calculate odds ratios
summLogistic <- function(mod){
  co.tab <- summary(mod)$coef

  or <- exp(co.tab[,1])
  up <- exp(co.tab[,1]+1.96*co.tab[,2])
  lo <- exp(co.tab[,1]-1.96*co.tab[,2])

  c1 <- paste(round(co.tab[,1],2)," (",round(co.tab[,2],3),")",sep="")
  c2 <- paste(round(or,2)," (",round(lo,3),",
",round(up,3),")",sep="")
  c3 <- round(co.tab[,4],3)
```

```
  zero.id <- which(c3==0)
  if(length(zero.id)>0) c3[zero.id] <- "<0.001"

  res <- data.frame(cbind(c1,c2,c3))
  names(res) <- c("est (se)","OR (95% CI)","Pval")

  res
}

#Individual variable odds ratio's risks
variable.model <- glm(sur_scan_in_18months ~ `year of op`+`year of
op`^5, data = train.data, family = binomial)
summLogistic(variable.model)
variable.model <-glm (sur_scan_in_18months ~ `factor_year_of_op`, data
= train.data, family = binomial)
summLogistic(variable.model)
variable.model <- glm(sur_scan_in_18months ~ pt_age_at_operation, data
= train.data, family = binomial)
summLogistic(variable.model)
variable.model <- glm(sur_scan_in_18months ~ gender, data =
train.data, family = binomial)
summLogistic(variable.model)
variable.model <- glm(sur_scan_in_18months ~ distance_factor, data =
train.data, family = binomial)
summLogistic(variable.model)
variable.model <- glm(sur_scan_in_18months ~ distance, data =
train.data, family = binomial)
summLogistic(variable.model)
variable.model <- glm(sur_scan_in_18months ~ `max pre-op diameter`,
data = train.data, family = binomial)
summLogistic(variable.model)
variable.model <- glm(sur_scan_in_18months ~ time, data = train.data,
family = binomial)
summLogistic(variable.model)
variable.model <- glm(sur_scan_in_18months ~ time_factor, data =
train.data, family = binomial)
summLogistic(variable.model)
variable.model <- glm(sur_scan_in_18months ~ si_before, data =
train.data, family = binomial)
summLogistic(variable.model)
variable.model <- glm(sur_scan_in_18months ~ `age at time`, data =
train.data, family = binomial)
summLogistic(variable.model)

#Remove data with missing point
train.data <- na.omit(train.data)
#create a full (adjusted) model
full.model <- glm(sur_scan_in_18months ~`age at time`+`time`+`year of
op`+`age at op`+`gender`+`distance`+`si_before`+`max pre-op diameter`,
data = train.data, family = binomial)
#odds ratios of the full model
summLogistic(full.model)

#stepwise regression to remove less important and confounding
veriables
step.model <- stepAIC(full.model)
#odds ratios of stepwise (simplfied) model
summLogistic(step.model)

#ensure stepwise regression hasn't significantly effected predictive
power
#Full model
```

```
# Make predictions
test.data <- na.omit(test.data)
probabilities <- full.model %>% predict(test.data, type = "response")
predicted.classes <- ifelse(probabilities > 0.5, TRUE , FALSE)
# Prediction accuracy
observed.classes <- test.data$sur_scan_in_18months
mean(predicted.classes == observed.classes)
#Step Model
# Make predictions
probabilities <- step.model %>% predict(test.data, type = "response")
predicted.classes <- ifelse(probabilities > 0.5, TRUE , FALSE)
# Prediction accuracy
observed.classes <- test.data$sur_scan_in_18months
mean(predicted.classes == observed.classes)

## complete for local patients only
training.samples <- local_patients$Database.ID %>%
createDataPartition(p = 0.8, list = FALSE)
lptrain.data  <- local_patients[training.samples,c(2:15)]
lptest.data <- local_patients[-training.samples,c(2:15)]

#Remove data with missing point
lptrain.data <- na.omit(lptrain.data)
#create a full (adjusted) model
full.model <- glm(sur_scan_in_18months ~`age at
time`+time+factor_year_of_op+. , data = lptrain.data, family =
binomial)
#odds ratios of the full model
summLogistic(full.model)

#stepwise regression to remove less important and confounding
veriables
step.model <- stepAIC(full.model)
#odds ratios of stepwise (simplfied) model
summLogistic(step.model)
step.model$anova


#tidy
rm(probabilities, predicted.classes,observed.classes,step.model,
full.model, test.data, train.data, lptest.data,
lptrain.data,training.samples, variable.model)


### Data Manipulation for Surveillance Scan analysis ##
##AXR Data##
rm(AXR)
AXR <- subset(all_scans, !is.na(AXR.Baseline))
AXR <-AXR[,c(1:17)]
AXR <- AXR %>% arrange(Time.since.Operation.in.Years)
AXR <- AXR %>% arrange(Database.ID)
#Create a cumulative finding for "any abnormality"
AXR <- left_join(AXR,AXR, by="Database.ID", no.dups = FALSE)
AXR$calculation <- (AXR$Time.since.Operation.in.Years.x -
AXR$Time.since.Operation.in.Years.y)
AXR$calculation <- ifelse(is.na(AXR$calculation), 100,
AXR$calculation)
AXR <- subset(AXR, AXR$calculation >=0)
AXR$abnormal_any_time <- as.logical (AXR$AXR.Abnormal.x +
AXR$AXR.Abnormal.y)
AXR <- AXR %>% arrange(Time.since.Operation.in.Years.x)
AXR <- arrange(AXR, desc(abnormal_any_time))
```

```
AXR <- distinct(AXR, Database.ID, Time.since.Operation.in.Years.x,
.keep_all = TRUE)
AXR <-AXR[,c(1:17,35)]
names <- names(AXR)
names <- str_remove(names,fixed(".x"))
names(AXR) <- names
rm(names)
AXR <- AXR %>% arrange(Time.since.Operation.in.Years)
AXR <- AXR %>% arrange(Database.ID)
#Create a cumulative finding for migration
AXR <- left_join(AXR,AXR, by="Database.ID", no.dups = FALSE)
AXR$calculation <- (AXR$Time.since.Operation.in.Years.x -
AXR$Time.since.Operation.in.Years.y)
AXR <- subset(AXR, AXR$calculation >=0)
AXR$migration_any_time <- as.logical (AXR$AXR.Migration.x +
AXR$AXR.Migration.y)
AXR <- AXR %>% arrange(Time.since.Operation.in.Years.x)
AXR <- arrange(AXR, desc(migration_any_time))
AXR <- distinct(AXR, Database.ID, Time.since.Operation.in.Years.x,
.keep_all = TRUE)
AXR <-AXR[,c(1:18,37)]
names <- names(AXR)
names <- str_remove(names,fixed(".x"))
names(AXR) <- names
rm(names)
AXR <- AXR %>% arrange(Time.since.Operation.in.Years)
AXR <- AXR %>% arrange(Database.ID)
#Create a cumulative finding for any limb kink (bilateral)
AXR <- left_join(AXR,AXR, by="Database.ID", no.dups = FALSE)
AXR$calculation <- (AXR$Time.since.Operation.in.Years.x -
AXR$Time.since.Operation.in.Years.y)
AXR <- subset(AXR, AXR$calculation >=0)
AXR$any_limb_kink_any_time <- as.logical (AXR$AXR.Left.Limb.Kink.x +
AXR$AXR.Left.Limb.Kink.y + AXR$AXR.Right.Limb.Kink.x +
AXR$AXR.Right.Limb.Kink.y)
AXR <- AXR %>% arrange(Time.since.Operation.in.Years.x)
AXR <- arrange(AXR, desc(any_limb_kink_any_time))
AXR <- distinct(AXR, Database.ID, Time.since.Operation.in.Years.x,
.keep_all = TRUE)
AXR <-AXR[,c(1:19,39)]
names <- names(AXR)
names <- str_remove(names,fixed(".x"))
names(AXR) <- names
rm(names)
AXR <- AXR %>% arrange(Time.since.Operation.in.Years)
AXR <- AXR %>% arrange(Database.ID)
#Create a cumulative finding for any structural failure
AXR <- left_join(AXR,AXR, by="Database.ID", no.dups = FALSE)
AXR$calculation <- (AXR$Time.since.Operation.in.Years.x -
AXR$Time.since.Operation.in.Years.y)
AXR <- subset(AXR, AXR$calculation >=0)
AXR$any_structural_failure <- as.logical (AXR$AXR.Structural.Failure.x
+ AXR$AXR.Structural.Failure.y)
AXR <- AXR %>% arrange(Time.since.Operation.in.Years.x)
AXR <- arrange(AXR, desc(any_structural_failure))
AXR <- distinct(AXR, Database.ID, Time.since.Operation.in.Years.x,
.keep_all = TRUE)
AXR <-AXR[,c(1:20,41)]
names <- names(AXR)
names <- str_remove(names,fixed(".x"))
names(AXR) <- names
rm(names)
AXR <- AXR %>% arrange(Time.since.Operation.in.Years)
```

```
AXR <- AXR %>% arrange(Database.ID)
#Create a cumulative finding for any effacement
AXR <- left_join(AXR,AXR, by="Database.ID", no.dups = FALSE)
AXR$calculation <- (AXR$Time.since.Operation.in.Years.x -
AXR$Time.since.Operation.in.Years.y)
AXR <- subset(AXR, AXR$calculation >=0)
AXR$any_effacement <- as.logical (AXR$AXR.Effacement.x +
AXR$AXR.Effacement.y)
AXR <- AXR %>% arrange(Time.since.Operation.in.Years.x)
AXR <- arrange(AXR, desc(any_effacement))
AXR <- distinct(AXR, Database.ID, Time.since.Operation.in.Years.x,
.keep_all = TRUE)
AXR <-AXR[,c(1:21,43)]
names <- names(AXR)
names <- str_remove(names,fixed(".x"))
names(AXR) <- names
rm(names)
AXR <- AXR %>% arrange(Time.since.Operation.in.Years)
AXR <- AXR %>% arrange(Database.ID)
AXR <- AXR [,c(1,3,2,8:22)]
##AXR data##

##CDUS Data##
rm(CDUS)
CDUS <- subset(all_scans, !is.na(CDUS.Diagnostic))
CDUS <- CDUS[,c(1:4,18:31)]
#Create GRaft related endoleak TRUE/FALSE
CDUS$graft_related_unknown_endoleak <-
ifelse(CDUS$CDUS.Endoleak.Type=="Type
III"|CDUS$CDUS.Endoleak.Type=="Type IA"|CDUS$CDUS.Endoleak.Type=="Type
IB"|CDUS$CDUS.Endoleak.Type=="Other/Unknown",TRUE,FALSE)
#Create a Type II ENdoleak TRUE/FALSE
CDUS$typeII_endoleak <- ifelse(CDUS$CDUS.Endoleak.Type=="Type
II",TRUE,FALSE)
#Create a undiagnostic variable
CDUS$undiagnostic <- !CDUS$CDUS.Diagnostic
#Order Favorably for combining
CDUS <- CDUS %>% arrange(Time.since.Operation.in.Years)
CDUS <- CDUS %>% arrange(Database.ID)
#Create a cumulative finding for "CDUS Undiagnostic"
CDUS <- left_join(CDUS,CDUS, by="Database.ID", no.dups = FALSE)
CDUS$calculation <- (CDUS$Time.since.Operation.in.Years.x -
CDUS$Time.since.Operation.in.Years.y)
CDUS <- subset(CDUS, CDUS$calculation >=0)
CDUS$undiagnostic_any_time <- as.logical (CDUS$undiagnostic.x +
CDUS$undiagnostic.y)
CDUS <- CDUS %>% arrange(Time.since.Operation.in.Years.x)
CDUS <- arrange(CDUS, desc(undiagnostic_any_time))
CDUS <- distinct(CDUS, Database.ID, Time.since.Operation.in.Years.x,
.keep_all = TRUE)
CDUS <- CDUS[,c(1:21,43)]
names <- names(CDUS)
names <- str_remove(names,fixed(".x"))
names(CDUS) <- names
rm(names)
CDUS <- CDUS %>% arrange(Time.since.Operation.in.Years)
CDUS <- CDUS %>% arrange(Database.ID)
#Create a cumulative finding for "Any ENdoleak Present"
CDUS <- left_join(CDUS,CDUS, by="Database.ID", no.dups = FALSE)
CDUS$calculation <- (CDUS$Time.since.Operation.in.Years.x -
CDUS$Time.since.Operation.in.Years.y)
CDUS <- subset(CDUS, CDUS$calculation >=0)
```

```
CDUS$any_endoleak_any_time <- as.logical (CDUS$CDUS.Endoleak.Present.x
+ CDUS$CDUS.Endoleak.Present.y)
CDUS <- CDUS %>% arrange(Time.since.Operation.in.Years.x)
CDUS <- arrange(CDUS, desc(any_endoleak_any_time))
CDUS <- distinct(CDUS, Database.ID, Time.since.Operation.in.Years.x,
.keep_all = TRUE)
CDUS <- CDUS[,c(1:22,45)]
names <- names(CDUS)
names <- str_remove(names,fixed(".x"))
names(CDUS) <- names
rm(names)
CDUS <- CDUS %>% arrange(Time.since.Operation.in.Years)
CDUS <- CDUS %>% arrange(Database.ID)
#Create a cumulative finding for "Graft related / Unknown Endoleak"
CDUS <- left_join(CDUS,CDUS, by="Database.ID", no.dups = FALSE)
CDUS$calculation <- (CDUS$Time.since.Operation.in.Years.x -
CDUS$Time.since.Operation.in.Years.y)
CDUS <- subset(CDUS, CDUS$calculation >=0)
CDUS$graft_related_unknown_endoleak_any_time <- as.logical
(CDUS$graft_related_unknown_endoleak.x +
CDUS$graft_related_unknown_endoleak.y)
CDUS <- CDUS %>% arrange(Time.since.Operation.in.Years.x)
CDUS <- arrange(CDUS, desc(graft_related_unknown_endoleak_any_time))
CDUS <- distinct(CDUS, Database.ID, Time.since.Operation.in.Years.x,
.keep_all = TRUE)
CDUS <- CDUS[,c(1:23,47)]
names <- names(CDUS)
names <- str_remove(names,fixed(".x"))
names(CDUS) <- names
CDUS <- CDUS %>% arrange(Time.since.Operation.in.Years)
CDUS <- CDUS %>% arrange(Database.ID)
#Create a cumulative finding for "Type II Endoleak"
CDUS <- left_join(CDUS,CDUS, by="Database.ID", no.dups = FALSE)
CDUS$calculation <- (CDUS$Time.since.Operation.in.Years.x -
CDUS$Time.since.Operation.in.Years.y)
CDUS <- subset(CDUS, CDUS$calculation >=0)
CDUS$typeII_endoleak_any_time <- as.logical (CDUS$typeII_endoleak.x +
CDUS$typeII_endoleak.y)
CDUS <- CDUS %>% arrange(Time.since.Operation.in.Years.x)
CDUS <- arrange(CDUS, desc(typeII_endoleak_any_time))
CDUS <- distinct(CDUS, Database.ID, Time.since.Operation.in.Years.x,
.keep_all = TRUE)
CDUS <- CDUS[,c(1:24,49)]
names <- names(CDUS)
names <- str_remove(names,fixed(".x"))
names(CDUS) <- names
rm(names)
CDUS <- CDUS %>% arrange(Time.since.Operation.in.Years)
CDUS <- CDUS %>% arrange(Database.ID)
#Create a cumulative finding for "Limb Complication"
CDUS <- left_join(CDUS,CDUS, by="Database.ID", no.dups = FALSE)
CDUS$calculation <- (CDUS$Time.since.Operation.in.Years.x -
CDUS$Time.since.Operation.in.Years.y)
CDUS <- subset(CDUS, CDUS$calculation >=0)
CDUS$limb_complication_any_time <-
as.logical(CDUS$CDUS.Limb.Complication.x +
CDUS$CDUS.Limb.Complication.y)
CDUS <- CDUS %>% arrange(Time.since.Operation.in.Years.x)
CDUS <- arrange(CDUS, desc(limb_complication_any_time))
CDUS <- distinct(CDUS, Database.ID, Time.since.Operation.in.Years.x,
.keep_all = TRUE)
CDUS <- CDUS[,c(1:25,51)]
names <- names(CDUS)
```

```
names <- str_remove(names,fixed(".x"))
names(CDUS) <- names
rm(names)
CDUS <- CDUS %>% arrange(Time.since.Operation.in.Years)
CDUS <- CDUS %>% arrange(Database.ID)

#Create a cumulative finding for smallest aneurysm size in
surveillance
CDUS <- left_join(CDUS,CDUS, by="Database.ID", no.dups = FALSE)
CDUS$smallest_AAA_years_ago <- (CDUS$Time.since.Operation.in.Years.x -
CDUS$Time.since.Operation.in.Years.y)
CDUS <- subset(CDUS, CDUS$smallest_AAA_years_ago >=0)
CDUS$smallest_AAA_size_any_time <- ifelse(CDUS$CDUS.AAA.size.in.mm.x
<= CDUS$CDUS.AAA.size.in.mm.y, CDUS$CDUS.AAA.size.in.mm.x,
CDUS$CDUS.AAA.size.in.mm.y)
CDUS$smallest_AAA_size_any_time <-
ifelse(is.na(CDUS$smallest_AAA_size_any_time),
CDUS$CDUS.AAA.size.in.mm.x, CDUS$smallest_AAA_size_any_time)
CDUS$smallest_AAA_size_any_time <-
ifelse(is.na(CDUS$smallest_AAA_size_any_time),
CDUS$CDUS.AAA.size.in.mm.y, CDUS$smallest_AAA_size_any_time)
CDUS <- CDUS %>% arrange(Time.since.Operation.in.Years.x)
CDUS <- arrange(CDUS, smallest_AAA_size_any_time)
CDUS <- distinct(CDUS, Database.ID, Time.since.Operation.in.Years.x,
.keep_all = TRUE)
CDUS <- CDUS[,c(1:26,52,53)]
names <- names(CDUS)
names <- str_remove(names,fixed(".x"))
names(CDUS) <- names
rm(names)
CDUS <- CDUS %>% arrange(Time.since.Operation.in.Years)
CDUS <- CDUS %>% arrange(Database.ID)
#Create a size measurement for previous CDUS over 3 months ago
CDUS <- left_join(CDUS,CDUS, by="Database.ID", no.dups = FALSE)
CDUS$last_AAA_size_years_ago <- (CDUS$Time.since.Operation.in.Years.x
- CDUS$Time.since.Operation.in.Years.y)
CDUS$previous_AAA_size <- ifelse(CDUS$last_AAA_size_years_ago >=0.25,
CDUS$CDUS.AAA.size.in.mm.y, NA)
CDUS <- subset(CDUS, CDUS$last_AAA_size_years_ago >=0)
CDUS$last_AAA_size_years_ago <- ifelse(CDUS$last_AAA_size_years_ago
>=0.25, CDUS$last_AAA_size_years_ago, NA)
CDUS <- CDUS %>% arrange(last_AAA_size_years_ago)
CDUS <- distinct(CDUS, Database.ID, Time.since.Operation.in.Years.x,
.keep_all = TRUE)
CDUS <- CDUS[,c(1:28,56,57)]
names <- names(CDUS)
names <- str_remove(names,fixed(".x"))
names(CDUS) <- names
rm(names)
CDUS <- CDUS %>% arrange(Time.since.Operation.in.Years)
CDUS <- CDUS %>% arrange(Database.ID)

## Add AXR data onto CDUS
CDUS_AXR <- left_join(CDUS,AXR, by="Database.ID", no.dups = FALSE)
CDUS_AXR$calculated <- (CDUS_AXR$Time.since.Operation.in.Years.x -
CDUS_AXR$Time.since.Operation.in.Years.y)
CDUS_AXR$calculated <- ifelse(is.na(CDUS_AXR$calculated), 100,
CDUS_AXR$calculated)
CDUS_AXR$calculated <- ifelse(CDUS_AXR$calculated < 0, 100,
CDUS_AXR$calculated)
CDUS_AXR <- subset(CDUS_AXR, CDUS_AXR$calculated >=0)
CDUS_AXR <- CDUS_AXR %>% arrange(calculated)
```

```
CDUS_AXR <- distinct(CDUS_AXR, Database.ID,
Time.since.Operation.in.Years.x, .keep_all = TRUE)
a <- subset(CDUS_AXR, CDUS_AXR$calculated ==100)
a[,c(31:48)] <- NA
CDUS_AXR  <-rbind(subset(CDUS_AXR, CDUS_AXR$calculated !=100),a)
rm(a)

#Combine CDUS_AXR Data with Secondary Intervention Data
CDUS_AXR_si <- left_join(CDUS_AXR, secondary_interventions,
by="Database.ID", no.dups = FALSE)
CDUS_AXR_si$time_to_prev_si_in_years <-
(CDUS_AXR_si$Time.since.Operation.in.Years -
CDUS_AXR_si$Time.since.Operation.in.Years.x)
CDUS_AXR_si$previous_si <- ifelse(CDUS_AXR_si$time_to_prev_si_in_years
< 0, TRUE, FALSE)
CDUS_AXR_si$previous_si <- ifelse(is.na(CDUS_AXR_si$previous_si),
FALSE, CDUS_AXR_si$previous_si)
CDUS_AXR_si <- CDUS_AXR_si %>% arrange(desc(previous_si))
CDUS_AXR_si <- distinct(CDUS_AXR_si, Database.ID,
Time.since.Operation.in.Years.x, .keep_all = TRUE)

CDUS_AXR_si <- left_join(CDUS_AXR_si, secondary_interventions,
by="Database.ID", no.dups = FALSE)
CDUS_AXR_si$time_to_si_in_years_x <-
(CDUS_AXR_si$Time.since.Operation.in.Years.x.x -
CDUS_AXR_si$Time.since.Operation.in.Years.x)
a <- subset(CDUS_AXR_si, CDUS_AXR_si$time_to_si_in_years_x >= 0)
a$next_si <- TRUE
b <- subset(CDUS_AXR_si, is.na(CDUS_AXR_si$time_to_si_in_years_x))
c <- subset(CDUS_AXR_si, CDUS_AXR_si$time_to_si_in_years_x < 0)
CDUS_AXR_si <-rbind(b,c)
CDUS_AXR_si$next_si <- FALSE
CDUS_AXR_si <-rbind(CDUS_AXR_si,a)
rm(a,b,c)
CDUS_AXR_si <- CDUS_AXR_si %>% arrange(time_to_si_in_years_x)
CDUS_AXR_si <- distinct(CDUS_AXR_si, Database.ID,
Time.since.Operation.in.Years.x, .keep_all = TRUE)
CDUS_AXR_si <- CDUS_AXR_si[,c(1:59)]
CDUS_AXR_si <- CDUS_AXR_si %>%
arrange(Time.since.Operation.in.Years.x)
CDUS_AXR_si <- CDUS_AXR_si %>% arrange(Database.ID)

#Combine AXR & CDUS with patient level data
data <- merge (CDUS_AXR_si ,patient_data, by="Database.ID")
data$smallest_AAA_size_any_time <-
ifelse(is.na(data$smallest_AAA_size_any_time),
data$Max.Pre.op.Iliac.Diameter.in.mm, data$smallest_AAA_size_any_time)
data$max_growth <- data$CDUS.AAA.size.in.mm-
data$smallest_AAA_size_any_time
data$recent_growth <- data$CDUS.AAA.size.in.mm -
data$previous_AAA_size
data$recent_growth_rate <-
data$recent_growth/data$last_AAA_size_years_ago
data$axr_delay <- data$Time.since.Operation.in.Years.x -
data$Time.since.Operation.in.Years.y
data$limb_kink <- as.logical (data$AXR.Left.Limb.Kink +
data$AXR.Right.Limb.Kink)

all_data$op_end <-
all_data$Time.from.operation.to.Start.of.Observational.period.in.Years
+ 7
```

```
all_data$Time.from.Operation.to.No.Follow.Up.in.Years <-
ifelse(is.na(all_data$Time.from.Operation.to.No.Follow.Up.in.Years),
1000, all_data$Time.from.Operation.to.No.Follow.Up.in.Years)
all_data$time <- ifelse(all_data$op_end <
all_data$Time.from.Operation.to.No.Follow.Up.in.Years,
all_data$op_end,
all_data$Time.from.Operation.to.No.Follow.Up.in.Years)
all_data$Time.from.Operation.to.Death.in.Years <-
ifelse(is.na(all_data$Time.from.Operation.to.Death.in.Years), 1000,
all_data$Time.from.Operation.to.Death.in.Years)
all_data$time <- ifelse(all_data$time <
all_data$Time.from.Operation.to.Death.in.Years, all_data$time,
all_data$Time.from.Operation.to.Death.in.Years)
all_data$Time.since.Operation.in.Years.y <-
ifelse(is.na(all_data$Time.since.Operation.in.Years.y),1000,all_data$T
ime.since.Operation.in.Years.y)
all_data$time <- all_data$time -
all_data$Time.since.Operation.in.Years.x
all_data <- subset(all_data, time>0)

all_data$time_to_si_in_years <-
all_data$Time.since.Operation.in.Years.x.x -
all_data$Time.since.Operation.in.Years.x
all_data$time_to_si_in_years <- ifelse(all_data$time_to_si_in_years<0,
NA, all_data$time_to_si_in_years)

all_data$event <- ifelse(all_data$time_to_si_in_years <=
all_data$time, TRUE, FALSE)
all_data$event <- ifelse(is.na(all_data$event),FALSE,all_data$event)
all_data$time <- ifelse(all_data$event==TRUE,
all_data$time_to_si_in_years,all_data$time)

all_data <- all_data %>% mutate_all(na_if,"")

DATA <- data.frame(all_data$Database.ID,
all_data$Time.since.Operation.in.Years.x,all_data$undiagnostic,all_dat
a$undiagnostic_any_time,all_data$CDUS.Endoleak.Present,all_data$any_en
doleak_any_time,all_data$graft_related_unknown_endoleak,all_data$graft
_related_unknown_endoleak_any_time,all_data$typeII_endoleak,all_data$t
ypeII_endoleak_any_time,all_data$CDUS.Limb.Complication,all_data$limb_
complication_any_time,all_data$CDUS.Mixed.Thrombose.in.AAA,all_data$CD
US.AAA.size.in.mm,all_data$max_growth,all_data$recent_growth,all_data$
recent_growth_rate,all_data$axr_delay,all_data$AXR.Abnormal,all_data$a
bnormal_any_time,all_data$AXR.Migration,all_data$migration_any_time,al
l_data$limb_kink,all_data$any_limb_kink_any_time,all_data$AXR.Structur
al.Failure,all_data$any_structural_failure,all_data$AXR.Effacement,all
_data$any_effacement,all_data$previous_si,all_data$Calander.Year.of.Op
eration,all_data$Age.at.Operation.in.Years,all_data$Gender,all_data$Di
stance.to.Surveillance.Centre.in.km,all_data$Max.Pre.op.Diameter.in.mm
,all_data$time,all_data$event,all_data$SI_Type.x,all_data$Patient.Symp
tomatic.x, all_data$Detected.on.Surveillance.x)
names(DATA) =
c("pt_id","time_since_op","cdus_undiagnostic","cdus_undiagnostic_cumul
ative", "cdus_any_endoleak",
"cdus_any_endoleak_cumulative","cdus_gru_endoleak","cdus_gru_endoleak_
cumulative","cdus_t2_endoleak","cdus_t2_endoleak_cumulative","cdus_lim
bs","cdus_limbs_cumulative",
"cdus_mixed_thrombus","cdus_aaa_size","cdus_max_growth","cdus_recent_g
rowth","cdus_recent_growth_rate",
"axr_delay","axr_abnormal","axr_abnormal_cumulative","axr_migration","
axr_migration_cumulative","axr_limb_kink","axr_limb_kink_cumulative","
axr_structural","axr_structural_cumulative","axr_effacement","axr_effa
cement_cumulative","pt_previous_si","pt_year_of_operation","pt_age_at_
```

```
operation","pt_sex","pt_distance_to_surveillance","pt_max_preop_AAA_si
ze","follow_up_time", "event", "si_type",
"symptomatic","surv_detected")

###Description of Variables in DATA###
#pt_id                          patient unique identifier
#time_since_op                  years after opertaion that CDUS
(Ultrasound) occured
#cdus_diagnostic                this CDUS (Ultrasound) was not
diagnostic (TRUE) or diagnostic (FALSE)
#cdus_undiagnostic_cumulative   any (previous or current) CDUS was not
diagnostic (TRUE) or all were diagnostic (FALSE)
#cdus_any_endoleak              any endoleak detected (TRUE) or none
(FALSE) on this CDUS (Ultrasound)
#cdus_any_endoleak_cumulative   any endoleak detected (TRUE) or none
(FALSE) on any (previous or current) CDUS
#cdus_gru_endoleak              graft-related or unknown source
endoleak detected (TRUE) or none (FALSE) on this CDUS (Ultrasound)
#cdus_gru_endoleak_cumulative   graft-related or unknown source
endoleak detected (TRUE) or none (FALSE) on any (previous or current)
CDUS
#cdus_t2_endoleak               type II endoleak detected (TRUE) or
none (FALSE) on this CDUS (Ultrasound)
#cdus_t2_endoleak_cumulative    type II endoleak detected (TRUE) or
none (FALSE) on any (previous or current) CDUS
#cdus_limbs                     any limb finding (TRUE) or none
(FALSE) on this CDUS (Ultrasound)
#cdus_limbs_cumulative          any limb finding (TRUE) or none
(FALSE) on any (previous or current) CDUS
#cdus_mixed_thrombus            thrombus between EVAR stent-graft &
AAA wall is hetrogenous (TRUE) or Homogenous (FALSE) on this CDUS
#cdus_aaa_size                  max aaa diameter (mm) on this CDUS
(ultrasound)
#cdus_max_growth                difference in diameter (mm) between
current CDUS and smallest diameter measured
#cdus_recent_growth             difference in diameter (mm) between
current CDUS and last CDUS (which must have been over 0.25 years ago)
#cdus_recent_growth_rate        growth rate (mm/year) between current
CDUS and last CDUS (which must have been over 0.25 years ago)
#axr_delay                      number of years beofre CDUS that AXR
(x-ray) was performed
#axr_abnormal                   any abnormality detected (TRUE) or not
(FALSE) on this AXR (x-ray)
#axr_abnormal_cumulative        any abnormality detected (TRUE) or not
(FALSE) on any (previous or current) AXR
#axr_migration                  any migration detected (TRUE) or not
(FALSE) on this AXR (x-ray)
#axr_migration_cumulative       any migration detected (TRUE) or not
(FALSE) on any (previous or current) AXR
#axr_limb_kink                  any limb kink detected (TRUE) or not
(FALSE) on this AXR (x-ray)
#axr_limb_kink_cumulative       any limb kink detected (TRUE) or not
(FALSE) on any (previous or current) AXR
#axr_structural                 any structural failure detected (TRUE)
or not (FALSE) on this AXR (x-ray)
#axr_structural_cumulative      any structural failure detected (TRUE)
or not (FALSE) on any (previous or current) AXR
#axr_effacement                 any effacement detected (TRUE) or not
(FALSE) on this AXR (x-ray)
#axr_effacement_cumulative      any effacement detected (TRUE) or not
(FALSE) on any (previous or current) AXR
#pt_previous_si                 has the patient previously undergone
(TRUE) or not (FALSE) a secondary intervention
```

```
#pt_year_of_operation           the calander year the primary EVAR was
performed in
#pt_age_at_operation            the patients age at the time of the
primary EVAR
#pt_sex                         patients recorded sex (Male/Female)
#pt_distance_to_surveillance    distance (km) from patients last
recorded address to surveillance centre
#pt_max_preop_AAA_size          max diameter (mm) measured pre-op
#follow_up_time                 time (years) between scan and end of
observation
#event                          secondary intervention (TRUE) or
censored (FALSE)
#si_type                        secondary intervention Flow or
Aneurysm related
#symptomatic                    was the patient symptomatic at time of
SI
#surv_deteceted                 was the SI triggered by surveillance

##determining time frame over which surveillance scans raise
intervention rates above that of baseline
#Select dataset
DATA1 <- DATA
#Add in this line for data exclusing first 9 months after EVAR as by
far the highest re-intervention rate
#DATA1 <- subset(DATA1,DATA1$time_since_op>=0.75)
#Star of analyiss
DATA1 <- DATA1[order(DATA1$follow_up_time),]
#censor data at 2 years
x<-2 #correct with final value#
##Limit dat to timeframe "x"##
j <- 1:length(DATA1[,1])
for (i in j) {
  if (DATA1$follow_up_time[i] > x) {
    DATA1$follow_up_time[i] <- (x+0.00001)#survminer needs for at risk
table
    DATA1$event[i] <- FALSE
  } else {
    DATA1$follow_up_time[i] <- DATA1$follow_up_time[i]
    DATA1$event[i] <- DATA1$event[i]
  }
}
rm(x)
#basic data
str(unique(DATA1$pt_id))
summary(DATA1$event)
#Hazard Ratio Analysis for all data
x <- nelsonaalen(DATA1, follow_up_time, event)
plot <-data.frame(DATA1$follow_up_time,x,diff(c(0,x)))

un.time <- unique(plot[,1])
diff.time <- diff(c(0,un.time))


mod <- lm((plot[,2])~-
1+plot[,1]+I(plot[,1]^2)+I(plot[,1]^3)+I(plot[,1]^4)+I(plot[,1]^5)+I(p
lot[,1]^6)+I(plot[,1]^7))
anova(mod)

#### Differentiating
co <- coef(mod)
x <- plot[,1]
x.pow <- cbind(1,2*x,3*x^2,4*x^3,5*x^4,6*x^5,7*x^6)
diff <- (co)%*%t(x.pow)
```

```
fit.y <- log(t((coef(mod))%*%t(model.matrix(mod))))
##Cumulative Hazard Ratio
Cairo(file="cumulative_hazard_ratio.png", type="png",units="mm",
width= 140, height = 86.5, dpi=600, ponitsize="1")
plot(plot[,1],log(plot[,2]),ylab="log(Cumulative Hazard
Ratio)",xlab="Time After Surveillance Scan (Years)", xlim=c(0,1.2),
pch = 20, cex=0.4)
lines(plot[,1],fit.y,lwd=5,col=alpha(rgb(1,0,0), 0.5))
legend("bottom", legend=c("Absolute Values", "Best Fit
Line"),col=c("Black", alpha(rgb(1,0,0), 0.5)), lty=c(0,1), pch =
c(20,NA), lwd = c(NA,5))
dev.off()
#Point Hazard Ratio
Cairo(file="absolute_hazard_ratio.png", type="png",units="mm", width=
140, height = 86.5, dpi=600, ponitsize="1")
plot(plot[,1],diff,typ="l",lwd=5,col=alpha(rgb(1,0,0),
1),ylab="Absolute Point Hazard Ratio",xlab="Time After Surveillance
Scan (Years)", xlim=c(0,1.2), ylim=c(0,0.25))
abline(v=0.5,col="gray",lty=2)
legend("topright", legend="Best Fit Line",col=alpha(rgb(1,0,0), 1),
lty=1, lwd = 5)
dev.off()

rm(co,x,x.pow,diff,fit.y,DATA1)
# basic data
a<-subset(DATA1,time_since_op>=0.75)
str(a)
str(unique(a$pt_id))
summary(a$event)
subset(DATA1,time_since_op>=0.75)
#Hazard Ratio Analysis for scans performed after .75 years after
operation.
x <- nelsonaalen(subset(DATA1,time_since_op>=0.75), follow_up_time,
event)
plot <-
data.frame(subset(DATA1,time_since_op>=0.75)$follow_up_time,x,diff(c(0
,x)))
un.time <- unique(plot[,1])
diff.time <- diff(c(0,un.time))
mod <- lm((plot[,2])~-
1+plot[,1]+I(plot[,1]^2)+I(plot[,1]^3)+I(plot[,1]^4)+I(plot[,1]^5)+I(p
lot[,1]^6)+I(plot[,1]^7))
anova(mod)
#### Differentiating
co <- coef(mod)
x <- plot[,1]
x.pow <- cbind(1,2*x,3*x^2,4*x^3,5*x^4,6*x^5,7*x^6)
diff <- (co)%*%t(x.pow)
fit.y <- log(t((coef(mod))%*%t(model.matrix(mod))))
#check plot for anlysis for 0.75 year cohort
plot(plot[,1],log(plot[,2]),ylab="log(Cumulative Hazard
Ratio)",xlab="Time After Surveillance Scan (Years)", xlim=c(0,1.2),
pch = 20, cex=0.4)
lines(plot[,1],fit.y,lwd=5,col=alpha(rgb(1,0,0), 0.5))
#plot for best fir line for 0.75 year cohort
Cairo(file="absolute_hazard_ratio_late.png", type="png",units="mm",
width= 140, height = 86.5, dpi=600, ponitsize="1")
plot(plot[,1],diff,typ="l",lwd=5,col=alpha(rgb(1,0,0),
1),ylab="Absolute Point Hazard Ratio",xlab="Time After Surveillance
Scan (Years)", xlim=c(0,1.2), ylim=c(0,0.08))
abline(v=0.5,col="gray",lty=2)
legend("topright", legend="Best Fit Line",col=alpha(rgb(1,0,0), 1),
lty=1, lwd = 5)
```

```
dev.off()


##### As such time that surveillance scans felt to influence re-
intervention rates over was 0.5 years ###
## Add in AXR migration Factor##
migration_data <- read.csv("axr_migration_factor.csv", header = TRUE,
col.names = c("pt_id","time_since_op","migration_factor"))
DATA1 <- DATA
DATA1$axr_time <- DATA1$time_since_op - DATA1$axr_delay
DATA1 <- left_join (DATA1, migration_data,
by=c("pt_id","axr_time"="time_since_op"))
DATA1$migration_factor <-
ifelse(is.na(DATA1$axr_delay),NA,ifelse(is.na(DATA1$migration_factor),
"None",as.character(DATA1$migration_factor)))
DATA1$migration_factor <- as.factor(DATA1$migration_factor)
DATA1$migration_factor1 <- DATA1$migration_factor
DATA1$migration_factor1 <- ifelse(DATA1$migration_factor1=="Definite
Migration","Definite Migration","No Migration / Other")
DATA1$migration_factor1 <- ifelse(DATA1$migration_factor1=="Definite
Migration", TRUE, FALSE)

DATA1 <- DATA1[,c(1:39,41,42)]

x<-0.5
##Limit dat to timeframe "x"##
j <- 1:length(DATA1[,1])
for (i in j) {
  if (DATA1$follow_up_time[i] > x) {
    DATA1$follow_up_time[i] <- (x+0.00001)#survminer needs for at risk
table
    DATA1$event[i] <- FALSE
  } else {
    DATA1$follow_up_time[i] <- DATA1$follow_up_time[i]
    DATA1$event[i] <- DATA1$event[i]
  }
}

##Investigate findings associated with flow related secondary
intervention##
#Events only count if flow related - Otherwise cencored at right
censor or other si
DATA1$flow <- ifelse (DATA1$event==TRUE & DATA1$si_type=="Flow", TRUE,
FALSE)
DATA1$aneurysm <- ifelse (DATA1$event==TRUE &
DATA1$si_type=="Aneurysm", TRUE, FALSE)

#Create Multiple Imputations for NA's in DATA1 dataset
DATA1_MI <-
mice(DATA1[,c(2:36,40:43)],method=c("","","","","","","","","","","","
","pmm","pmm","pmm","pmm","pmm","logreg","logreg","logreg","","logreg"
,"","logreg","","logreg","","","","","","pmm","pmm","","","polyreg","l
ogreg","",""), m=50)
##NOTE## Cumulative AXR data excluded due to poor imputational output
#save(DATA1_MI, file="midata.RData")
#Load above Multiple Imputations data
load("midata.RData")

stripplot(DATA1_MI$data$cdus_recent_growth_rate, pch = 20, cex = 1.2)


#Basic data
str(DATA1$pt_id)
```

```
unique(DATA1$pt_id)
summary(DATA1$flow)
summary(DATA1$aneurysm)
#Related AXR data
summary(DATA1$axr_delay)

###CDUS Diagnostic - Flow - NOT SIgnificant
summary(DATA1$cdus_undiagnostic)#no missing data (no NA)
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$flow)~DATA1$cdus_undiagnostic,
data = DATA1)
Cairo(file="km_cdus_undiagnostic_flow.png", type="png",units="mm",
width= 177, height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("CDUS Diagnostic",
"CDUS Undiagnostic"), risk.table = TRUE, pval = TRUE, conf.int = TRUE,
break.time.by = 0.1, censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom From\n'Flow
Related'\nSecondary Intervention", surv.scale="percent", legend.title
= "Key: ", xlim = c(0, x), ylim=c(0.95,1), pval.coord = c(0.1, 0.96))
dev.off()
#CoxPH Model
coxph(Surv(DATA1$follow_up_time,DATA1$flow)~DATA1$cdus_undiagnostic)
exp(0.3540-(1.93*0.3356))
exp(0.3540+(1.93*0.3356))
#Hazard Ratio of 1.42 (0.74 - 2.72)
rm(fit)

###CDUS Diagnostic - Aneurysm - NOT SIgnificant
summary(DATA1$cdus_undiagnostic)#no missing data (no NA)
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_undiagnos
tic, data = DATA1)
Cairo(file="km_cdus_undiagnostic_aneurysm.png", type="png",units="mm",
width= 177, height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("CDUS Diagnostic",
"CDUS Undiagnostic"), risk.table = TRUE, pval = TRUE, conf.int = TRUE,
break.time.by = 0.1, censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom
From\n'Aneurysm Related'\nSecondary Intervention",
surv.scale="percent", legend.title = "Key: ", xlim = c(0, x),
ylim=c(0.95,1), pval.coord = c(0.1, 0.96))
dev.off()
#CoxPH Model
coxph(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_undiagnosti
c)
exp(0.1848-(1.93*0.4358))
exp(0.1848+(1.93*0.4358))
#Hazard Ratio of 0.83 (0.52 - 2.79)
rm(fit)

###CDUS Cumulative Diagnostic - Flow - NOT SIgnificant
summary(DATA1$cdus_undiagnostic_cumulative)#no missing data (no NA)
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$flow)~DATA1$cdus_undiagnostic_
cumulative, data = DATA1)
Cairo(file="km_cdus_undiagnostic_cumulative_flow.png",
type="png",units="mm", width= 177, height=115, dpi=600, ponitsize="1")
```

```
ggsurvplot(fit, legend = "bottom", legend.labs = c("All CDUS
Diagnostic", "\u2265 1 CDUS Undiagnostic"), risk.table = TRUE, pval =
TRUE, conf.int = TRUE, break.time.by = 0.1, censor=FALSE,
risk.table.title="Number at Risk", risk.table.y.text=FALSE,
risk.table.y.text.col=TRUE, risk.table.height = 0.4, xlab="Years Since
Surveillance Scan", ylab="Freedom From\n'Flow Related'\nSecondary
Intervention", surv.scale="percent", legend.title = "Key: ", xlim =
c(0, x), ylim=c(0.95,1), pval.coord = c(0.1, 0.96))
dev.off()
#CoxPH Model
coxph(Surv(DATA1$follow_up_time,DATA1$flow)~DATA1$cdus_undiagnostic_cu
mulative)
exp(-0.3941-(1.93*0.3077))
exp(-0.3941+(1.93*0.3077))
#Hazard Ratio of 0.67 (0.37 - 1.22)
rm(fit)

###CDUS Cumulative Diagnostic - Aneurysm -Significant
summary(DATA1$cdus_undiagnostic_cumulative)#no missing data (no NA)
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_undiagnos
tic_cumulative, data = DATA1)
Cairo(file="km_cdus_undiagnostic_aneurysm_cumulative.png",
type="png",units="mm", width= 177, height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("All CDUS
Diagnostic", "\u2265 1 CDUS Undiagnostic"), risk.table = TRUE, pval =
TRUE, conf.int = TRUE, break.time.by = 0.1, censor=FALSE,
risk.table.title="Number at Risk", risk.table.y.text=FALSE,
risk.table.y.text.col=TRUE, risk.table.height = 0.4, xlab="Years Since
Surveillance Scan", ylab="Freedom From\n'Aneurysm Related'\nSecondary
Intervention", surv.scale="percent", legend.title = "Key: ", xlim =
c(0, x), ylim=c(0.95,1), pval.coord = c(0.1, 0.96))
dev.off()
#CoxPH Model
coxph(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_undiagnosti
c_cumulative)
exp(-0.9054-(1.93*0.3865))
exp(-0.9054+(1.93*0.3865))
#Hazard Ratio of 0.40 (0.19 - 0.85)
rm(fit)

###CDUS Any Endoleak### - SIGNIFICANT
summary(DATA1$cdus_any_endoleak) # no missing data(no NA)
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_any_endol
eak, data = DATA1)
Cairo(file="km_cdus_any_endoleak_aneurysm.png", type="png",units="mm",
width= 177, height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("No Endoleak
Detected", "\u2265 1 Endoleak(s) Detected"), risk.table = TRUE, pval =
TRUE, conf.int = TRUE, break.time.by = 0.1, censor=FALSE,
risk.table.title="Number at Risk", risk.table.y.text=FALSE,
risk.table.y.text.col=TRUE, risk.table.height = 0.4, xlab="Years Since
Surveillance Scan", ylab="Freedom From\n'Aneurysm Related'\nSecondary
Intervention", surv.scale="percent", legend.title = "Key: ", xlim =
c(0, x), ylim=c(0.9,1), pval.coord = c(0.1, 0.925))
dev.off()
#CoxPH Model
coxph(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_any_endolea
k)
exp(2.1168-(1.93*0.2963))
```

```
exp(2.1168+(1.93*0.2963))
#  Harzard Ratio of 8.30 (4.69 - 14.71)
rm(fit)

###CDUS Any endoleak cumulative- much less effect
summary(DATA1$cdus_any_endoleak_cumulative)#no missing data (no NA)
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_any_endol
eak_cumulative, data = DATA1)
Cairo(file="km_cdus_any_endoleak_cumulative_aneurysm.png",
type="png",units="mm", width= 177, height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("No Endoleak Dected
on any CDUS", "\u2265 1 Endoleak(s) detected on any CDUS"), risk.table
= TRUE, pval = TRUE, conf.int = TRUE, break.time.by = 0.1,
censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom
From\n'Aneurysm Related'\nSecondary Intervention",
surv.scale="percent", legend.title = "Key: ", xlim = c(0, x),
ylim=c(0.95,1), pval.coord = c(0.05, 0.965))
dev.off()
#CoxPH Model
coxph(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_any_endolea
k_cumulative)
exp(1.6839-(1.93*0.3162))
exp(1.6839+(1.93*0.3162))
#Hazard Ratio of 5.38 (2.93 - 9.92)
rm(fit)


###CDUS GR Endoleak### - SIGNIFICANT
summary(DATA1$cdus_gru_endoleak) # no missing data(no NA)
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_gru_endol
eak, data = DATA1)
Cairo(file="km_cdus_gr_endoleak_aneurysm.png", type="png",units="mm",
width= 177, height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("No Graft Related
Endoleak Detected", "\u2265 1 Graft Related Endoleak(s) Detected"),
risk.table = TRUE, pval = TRUE, conf.int = TRUE, break.time.by = 0.1,
censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom
From\n'Aneurysm Related'\nSecondary Intervention",
surv.scale="percent", legend.title = "Key: ", xlim = c(0, x),
ylim=c(0.5,1), pval.coord = c(0.1, 0.6))
dev.off()
#CoxPH Model
coxph(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_gru_endolea
k)
exp(3.4173-(1.93*0.2934))
exp(3.4173+(1.93*0.2934))
#  Harzard Ratio of 30.49 (17.31 - 53.71)
rm(fit)

###CDUS GR endoleak cumulative- much less significant
summary(DATA1$cdus_gru_endoleak_cumulative)#no missing data (no NA)
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_gru_endol
eak_cumulative, data = DATA1)
```

```
Cairo(file="km_cdus_gr_endoleak_cumulative.png",
type="png",units="mm", width= 177, height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("No Graft Related
Endoleak Detected", "\u2265 1 Graft Related Endoleak(s) detected"),
risk.table = TRUE, pval = TRUE, conf.int = TRUE, break.time.by = 0.1,
censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom
From\n'Aneurysm Related'\nSecondary Intervention",
surv.scale="percent", legend.title = "Key: ", xlim = c(0, x),
ylim=c(0.85,1), pval.coord = c(0.05, 0.875))
dev.off()
#CoxPH Model
coxph(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_gru_endolea
k_cumulative)
exp(2.3533-(1.93*0.2873))
exp(2.3533+(1.93*0.2873))
#Hazard Ratio of 10.52 (6.04 - 18.32)
rm(fit)

###CDUS Type II Endoleak### - NOT SIGNIFICANT
summary(DATA1$cdus_t2_endoleak) # no missing data(no NA)
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_t2_endole
ak, data = DATA1)
Cairo(file="km_cdus_t2_endoleak_aneurysm.png", type="png",units="mm",
width= 177, height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("No Type II
Endoleak Detected", "\u2265 1 Type II Endoleak(s) Detected"),
risk.table = TRUE, pval = TRUE, conf.int = TRUE, break.time.by = 0.1,
censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom From\n
'Aneurysm Related'\nSecondary Intervention", surv.scale="percent",
legend.title = "Key: ", xlim = c(0, x), ylim=c(0.95,1), pval.coord =
c(0.1, 0.975))
dev.off()
#CoxPH Model
coxph(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_t2_endoleak
)
exp(0.6111-(1.93*0.3322))
exp(0.6111+(1.93*0.3322))
#  Harzard Ratio of 1.84 (0.97 - 3.50)
rm(fit)

###CDUS Type II endoleak cumulative- much less significant
summary(DATA1$cdus_t2_endoleak_cumulative)#no missing data (no NA)
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_t2_endole
ak_cumulative, data = DATA1)
Cairo(file="km_cdus_t2_endoleak_cumulative.png",
type="png",units="mm", width= 177, height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("No Type II
Endoleak Detected", "\u2265 1 Type II Endoleak(s) detected"),
risk.table = TRUE, pval = TRUE, conf.int = TRUE, break.time.by = 0.1,
censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom
From\n'Aneurysm Related'\nSecondary Intervention",
surv.scale="percent", legend.title = "Key: ", xlim = c(0, x),
ylim=c(0.95,1), pval.coord = c(0.05, 0.975))
```

```
dev.off()
#CoxPH Model
coxph(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_t2_endoleak
_cumulative)
exp(0.5171-(1.93*0.2932))
exp(0.5171+(1.93*0.2932))
#Hazard Ratio of 1.68 (0.95 - 2.95)
rm(fit)

###CDUS Limb ABnormality###
summary(DATA1$cdus_limbs) # no missing data(no NA)
#KM Graph for 'flow related'
fit <-survfit(Surv(DATA1$follow_up_time,DATA1$flow)~DATA1$cdus_limbs,
data = DATA1)
Cairo(file="km_cdus_limb_issue.png", type="png",units="mm", width=
177, height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("No Limb
abnormality detected on CDUS", "\u2265 1 Limb abnormality detected on
CDUS"), risk.table = TRUE, pval = TRUE, conf.int = TRUE, break.time.by
= 0.1, censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom From\n'Flow
Related'\nSecondary Intervention", surv.scale="percent", legend.title
= "Key: ", xlim = c(0, x), ylim=c(0.75,1), pval.coord = c(0.1, 0.8))
dev.off()
#CoxPH Model
coxph(Surv(DATA1$follow_up_time,DATA1$flow)~DATA1$cdus_limbs)
exp(2.704-(1.93*0.281))
exp(2.704+(1.93*0.281))
#  Harzard Ratio of 14.935 (8.69 - 25.70)
rm(fit)

###CDUS Limb abnormality cumulative- much less significant
summary(DATA1$cdus_limbs_cumulative)#no missing data (no NA)
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$flow)~DATA1$cdus_limbs_cumulat
ive, data = DATA1)
Cairo(file="km_cdus_limb_issue_cumulative.png", type="png",units="mm",
width= 177, height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("No Limb
abnormality detected on any CDUS", "\u2265 1 Limb abnormality detected
on any CDUS"), risk.table = TRUE, pval = TRUE, conf.int = TRUE,
break.time.by = 0.1, censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom From\n'Flow
Related'\nSecondary Intervention", surv.scale="percent", legend.title
= "Key: ", xlim = c(0, x), ylim=c(0.75,1), pval.coord = c(0.1, 0.8))
dev.off()
#CoxPH Model
coxph(Surv(DATA1$follow_up_time,DATA1$flow)~DATA1$cdus_limbs_cumulativ
e)
exp(2.164-(1.93*0.285))
exp(2.164+(1.93*0.285))
#Hazard Ratio of 8.71 (5.02 - 15.09)
rm(fit)


###CDUS AAA Size - Not Significant
summary(DATA1$cdus_aaa_size)#125 NA's
#Dummy variable for NA's-flow
DATA1$cdus_aaa_size_nadum <- ifelse(is.na(DATA1$cdus_aaa_size), 0, 1)
```

```
DATA1$cdus_aaa_size <- ifelse(DATA1$cdus_aaa_size_nadum==0, 0,
DATA1$cdus_aaa_size)
summary(coxph(Surv(DATA1$follow_up_time,DATA1$flow)~DATA1$cdus_aaa_siz
e_nadum/DATA1$cdus_aaa_size), method="breslow")
summary(coxph(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_aaa
_size_nadum/DATA1$cdus_aaa_size), method="breslow")
#Missing data is important to both flow and aneurysm related SI's

#Models using Multiple Imputated data for flow related SI
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,flow)~cdus_aaa_size))
pool_models <- pool(models)
summary<- summary(pool_models)
exp(summary$estimate)#Hazard Ratio
exp(summary$estimate-(1.93*summary$std.error))#Lower 95% CI
exp(summary$estimate+(1.93*summary$std.error))#Upper 95% CI
summary$p.value# p Value
#Hazard Ratio of 1.01 (0.99 - 1.02) p=0.41
rm(fit,models,pool_models,summary)

#Models using Multiple Imputated data for aneurysm related SI
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,aneurysm)~cdus_aaa_si
ze))
pool_models <- pool(models)
summary<- summary(pool_models)
exp(summary$estimate)#Hazard Ratio
exp(summary$estimate-(1.93*summary$std.error))#Lower 95% CI
exp(summary$estimate+(1.93*summary$std.error))#Upper 95% CI
summary$p.value# p Value
#Hazard Ratio of 1.04 (1.03 - 1.05) p<0.0001
rm(fit,models,pool_models,summary)

####CDUS max growth
summary(DATA1$cdus_max_growth)#125 NA's
#125 NA's
#Dummy variable for NA's
DATA1$cdus_max_growth_nadum <- ifelse(is.na(DATA1$cdus_max_growth), 0,
1)
DATA1$cdus_max_growth <- ifelse(DATA1$cdus_max_growth_nadum==0, 0,
DATA1$cdus_max_growth)
summary(coxph(Surv(DATA1$follow_up_time,DATA1$flow)~DATA1$cdus_max_gro
wth_nadum/DATA1$cdus_max_growth), method="breslow")
summary(coxph(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_max
_growth_nadum/DATA1$cdus_max_growth), method="breslow")

#Missing data is important in flow model
#Models using Multiple Imputated data for 'flow related' SI
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,flow)~cdus_max_growth
))
pool_models <- pool(models)
summary<- summary(pool_models)
exp(summary$estimate)#Hazard Ratio
exp(summary$estimate-(1.93*summary$std.error))#Lower 95% CI
exp(summary$estimate+(1.93*summary$std.error))#Upper 95% CI
summary$p.value# p Value
#Hazard Ratio of 0.81 (0.67 - 0.98) p=0.03
rm(fit,models,pool_models,summary)

#Model using Available data for 'aneurysm related' SI
DATA1$cdus_max_growth <- ifelse(DATA1$cdus_max_growth_nadum==0, NA,
DATA1$cdus_max_growth)
```

```
coxph(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_max_growth)
exp(0.06087-(1.93*0.01237))
exp(0.06087+(1.93*0.01237))
#Hazard Ratio of 1.06 (1.04 - 1.09) p<0.0001

###CDUS recent growth
summary(DATA1$cdus_recent_growth) #988 NA's
#Dummy variable for NA's
DATA1$cdus_recent_growth_nadum <-
ifelse(is.na(DATA1$cdus_recent_growth), 0, 1)
DATA1$cdus_recent_growth <- ifelse(DATA1$cdus_recent_growth_nadum==0,
0, DATA1$cdus_recent_growth)
summary(coxph(Surv(DATA1$follow_up_time,DATA1$flow)~DATA1$cdus_recent_
growth_nadum/DATA1$cdus_recent_growth), method="breslow")
summary(coxph(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_rec
ent_growth_nadum/DATA1$cdus_recent_growth), method="breslow")
#Missing data is  not missing at random

#Cox model with MI data for flow model
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,flow)~cdus_recent_gro
wth))
pool_models <- pool(models)
summary<- summary(pool_models)
exp(summary$estimate)#Hazard Ratio
exp(summary$estimate-(1.93*summary$std.error))#Lower 95% CI
exp(summary$estimate+(1.93*summary$std.error))#Upper 95% CI
summary$p.value# p Value
#Hazard Ratio of 1.03 (0.94 - 1.12) p=0.54
rm(fit,models,pool_models,summary)

#Models using Multiple Imputated data for 'aneurysm related SI
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,aneurysm)~cdus_recent
_growth))
pool_models <- pool(models)
summary<- summary(pool_models)
exp(summary$estimate)#Hazard Ratio
exp(summary$estimate-(1.93*summary$std.error))#Lower 95% CI
exp(summary$estimate+(1.93*summary$std.error))#Upper 95% CI
summary$p.value# p Value
#Hazard Ratio of 1.11 (1.07 - 1.16) p<0.0001
rm(fit,models,pool_models,summary)

###CDUS recent growth rate
summary(DATA1$cdus_recent_growth_rate) #988 NA's
#Dummy variable for NA's-flow
DATA1$cdus_recent_growth_rate_nadum <-
ifelse(is.na(DATA1$cdus_recent_growth_rate), 0, 1)
DATA1$cdus_recent_growth_rate <-
ifelse(DATA1$cdus_recent_growth_rate_nadum==0, 0,
DATA1$cdus_recent_growth)
summary(coxph(Surv(DATA1$follow_up_time,DATA1$flow)~DATA1$cdus_recent_
growth_rate_nadum/DATA1$cdus_recent_growth_rate), method="breslow")
summary(coxph(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$cdus_rec
ent_growth_rate_nadum/DATA1$cdus_recent_growth_rate),
method="breslow")
#Missing data is  not missing at random

#Models using Multiple Imputated data for 'flow related' SI
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,flow)~cdus_recent_gro
wth_rate))
```

```
pool_models <- pool(models)
summary<- summary(pool_models)
exp(summary$estimate)#Hazard Ratio
exp(summary$estimate-(1.93*summary$std.error))#Lower 95% CI
exp(summary$estimate+(1.93*summary$std.error))#Upper 95% CI
summary$p.value# p Value
#Hazard Ratio of 1.01 (0.95 - 1.07) p=0.82
rm(fit,models,pool_models,summary)

#Models using Multiple Imputated data for 'aneurysm related' SI
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,aneurysm)~cdus_recent
_growth_rate))
pool_models <- pool(models)
summary<- summary(pool_models)
exp(summary$estimate)#Hazard Ratio
exp(summary$estimate-(1.93*summary$std.error))#Lower 95% CI
exp(summary$estimate+(1.93*summary$std.error))#Upper 95% CI
summary$p.value# p Value
#Hazard Ratio of 1.06 (1.04 - 1.09) p<0.0001
rm(fit,models,pool_models,summary)

###AXR effacement
summary(DATA1$axr_effacement)# 76 NA's
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$axr_effacement
, data = DATA1)
Cairo(file="km_axr_effacement.png", type="png",units="mm", width= 177,
height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("No effacement
detected on AXR", "Effacement detected on AXR"), risk.table = TRUE,
pval = TRUE, conf.int = TRUE, break.time.by = 0.1, censor=FALSE,
risk.table.title="Number at Risk", risk.table.y.text=FALSE,
risk.table.y.text.col=TRUE, risk.table.height = 0.4, xlab="Years Since
Surveillance Scan", ylab="Freedom From\n'Aneurysm Related'\nSecondary
Intervention", surv.scale="percent", legend.title = "Key: ", xlim =
c(0, x), ylim=c(0.825,1), pval.coord = c(0.1, 0.85))
dev.off()
#Asessment for missingness
table(DATA1$axr_effacement,DATA1$aneurysm,useNA="always")
#Missing data is important
#Models using Multiple Imputated data
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,aneurysm)~axr_effacem
ent))
pool_models <- pool(models)
summary<- summary(pool_models)
exp(summary$estimate)#Hazard Ratio
exp(summary$estimate-(1.93*summary$std.error))#Lower 95% CI
exp(summary$estimate+(1.93*summary$std.error))#Upper 95% CI
summary$p.value# p Value
#Hazard Ratio of 7.03 (3.00 - 16.46) p<0.0001
rm(fit,models,pool_models,summary)

###AXR effacement cumulative
summary(DATA1$axr_effacement_cumulative)# 76 NA's
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$axr_effacement
_cumulative, data = DATA1)
Cairo(file="km_axr_effacement_cumulative.png", type="png",units="mm",
width= 177, height=115, dpi=600, ponitsize="1")
```

```
ggsurvplot(fit, legend = "bottom", legend.labs = c("No effacement
detected on any AXR", "Effacement detected on \u2265 1 AXR"),
risk.table = TRUE, pval = TRUE, conf.int = TRUE, break.time.by = 0.1,
censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom
From\n'Aneurysm Related'\nSecondary Intervention",
surv.scale="percent", legend.title = "Key: ", xlim = c(0, x),
ylim=c(0.925,1), pval.coord = c(0.1, 0.95))
dev.off()
#Asessment for missingness
table(DATA1$axr_effacement_cumulative,DATA1$aneurysm,useNA="always")
#Missing data is important
#Models using Multiple Imputated data
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,aneurysm)~axr_effacem
ent_cumulative))
pool_models <- pool(models)
summary<- summary(pool_models)
exp(summary$estimate)#Hazard Ratio
exp(summary$estimate-(1.93*summary$std.error))#Lower 95% CI
exp(summary$estimate+(1.93*summary$std.error))#Upper 95% CI
summary$p.value# p Value
#Hazard Ratio of 2.54 (1.14 - 5.64) p=0.02
rm(fit,models,pool_models,summary)

###AXR structural
summary(DATA1$axr_structural)# 76 NA's
#KM Graph aneurysm
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$axr_structural
, data = DATA1)
Cairo(file="km_axr_structural.png", type="png",units="mm", width= 177,
height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("No Structural
Failure detected on AXR", "Structural Failure detected on AXR"),
risk.table = TRUE, pval = TRUE, conf.int = TRUE, break.time.by = 0.1,
censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom
From\n'Aneurysm Related'\nSecondary Intervention",
surv.scale="percent", legend.title = "Key: ", xlim = c(0, x),
ylim=c(0.875,1), pval.coord = c(0.1, 0.9))
dev.off()
#Asessment for missingness
table(DATA1$axr_structural,DATA1$aneurysm,useNA="always")
#Models using Multiple Imputated data
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,aneurysm)~axr_structu
ral))
pool_models <- pool(models)
summary<- summary(pool_models)
exp(summary$estimate)#Hazard Ratio
exp(summary$estimate-(1.93*summary$std.error))#Lower 95% CI
exp(summary$estimate+(1.93*summary$std.error))#Upper 95% CI
summary$p.value# p Value
#Hazard Ratio of 4.16 (1.51 - 11.48) p=0.007
rm(fit,models,pool_models,summary)

###AXR structural cumulative
summary(DATA1$axr_structural_cumulative)# 76 NA's
#KM Graph
```

```
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$axr_structural
_cumulative, data = DATA1)
Cairo(file="km_axr_structural_cumulative.png", type="png",units="mm",
width= 177, height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("No structural
failure detected on any AXR", "Structural Failure detected on \u2265 1
AXR"), risk.table = TRUE, pval = TRUE, conf.int = TRUE, break.time.by
= 0.1, censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom
From\n'Aneurysm Related'\nSecondary Intervention",
surv.scale="percent", legend.title = "Key: ", xlim = c(0, x),
ylim=c(0.95,1), pval.coord = c(0.1, 0.965))
dev.off()
#Asessment for missingness
table(DATA1$axr_structural_cumulative,DATA1$aneurysm,useNA="always")
#Missing data is important
#Models using Multiple Imputated data
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,aneurysm)~axr_structu
ral_cumulative))
pool_models <- pool(models)
summary<- summary(pool_models)
exp(summary$estimate)#Hazard Ratio
exp(summary$estimate-(1.93*summary$std.error))#Lower 95% CI
exp(summary$estimate+(1.93*summary$std.error))#Upper 95% CI
summary$p.value# p Value
#Hazard Ratio of 1.53 (0.55 - 4.21) p=0.42
rm(fit,models,pool_models,summary)

###AXR limb kink - SIGNIFICANT
summary(DATA1$axr_limb_kink)# 76 NA's
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$flow)~DATA1$axr_limb_kink,
data = DATA1)
Cairo(file="km_axr_limb_issue.png", type="png",units="mm", width= 177,
height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("No Limb
abnormality detected on AXR", "\u2265 1 Limb abnormality detected on
AXR"), risk.table = TRUE, pval = TRUE, conf.int = TRUE, break.time.by
= 0.1, censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom From\n'Flow
Related'\nSecondary Intervention", surv.scale="percent", legend.title
= "Key: ", xlim = c(0, x), ylim=c(0.85,1), pval.coord = c(0.1, 0.875))
dev.off()
#assessment for missingness
table(DATA1$axr_limb_kink,DATA1$flow,useNA="always")
#Models using Multiple Imputated data
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,flow)~axr_limb_kink))
pool_models <- pool(models)
summary<- summary(pool_models)
exp(summary$estimate)#Hazard Ratio
exp(summary$estimate-(1.93*summary$std.error))#Lower 95% CI
exp(summary$estimate+(1.93*summary$std.error))#Upper 95% CI
summary$p.value# p Value
#Hazard Ratio of 4.32 (1.98 - 9.46) p=0.0003
rm(fit,models,pool_models,summary)
```

```
#AXR limb kink cumulative - NOT SIGNIFICANT
summary(DATA1$axr_limb_kink_cumulative)# 76 NA's
#KM Graph
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$flow)~DATA1$axr_limb_kink_cumu
lative, data = DATA1)
Cairo(file="km_axr_limb_issue_cumulative.png", type="png",units="mm",
width= 177, height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("No Limb
abnormality detected on any AXR", "\u2265 1 Limb abnormality detected
on any AXR"), risk.table = TRUE, pval = TRUE, conf.int = TRUE,
break.time.by = 0.1, censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom From\n'Flow
Related'\nSecondary Intervention", surv.scale="percent", legend.title
= "Key: ", xlim = c(0, x), ylim=c(0.94,1), pval.coord = c(0.1, 0.95))
dev.off()
#assessment for missingness
table(DATA1$axr_limb_kink_cumulative,DATA1$flow,useNA="always")
#Models using Multiple Imputated data
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,flow)~axr_limb_kink_c
umulative))
pool_models <- pool(models)
summary<- summary(pool_models)
exp(summary$estimate)#Hazard Ratio
exp(summary$estimate-(1.93*summary$std.error))#Lower 95% CI
exp(summary$estimate+(1.93*summary$std.error))#Upper 95% CI
summary$p.value# p Value
#Hazard Ratio of 1.80 (0.86 - 3.77) p=0.13
rm(fit,models,pool_models,summary)

#AXR migration factors
summary(DATA1$migration_factor)# 76 NA's
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$migration_fact
or, data = DATA1)
Cairo(file="km_migration_factor.png", type="png",units="mm", width=
177, height=125, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("Barb
Engagement","Definite Migration","Minor Migration","None","Unknown"),
risk.table = TRUE, pval = TRUE, conf.int = TRUE, break.time.by = 0.1,
censor=FALSE, risk.table.title="Number at Risk",
risk.table.y.text=FALSE, risk.table.y.text.col=TRUE, risk.table.height
= 0.4, xlab="Years Since Surveillance Scan", ylab="Freedom
From\n'Aneurysm Related'\nSecondary Intervention",
surv.scale="percent", legend.title = "Key: ", xlim = c(0, x),
ylim=c(0.85,1), pval.coord = c(0.1, 0.875))
dev.off()
#rationalised factor to denitine (TRUE/FALSE)
fit <-
survfit(Surv(DATA1$follow_up_time,DATA1$aneurysm)~DATA1$migration_fact
or2, data = DATA1)
Cairo(file="km_migration_definite.png", type="png",units="mm", width=
177, height=115, dpi=600, ponitsize="1")
ggsurvplot(fit, legend = "bottom", legend.labs = c("No Migration /
Other on AXR", "Definite Migration on AXR"), risk.table = TRUE, pval =
TRUE, conf.int = TRUE, break.time.by = 0.1, censor=FALSE,
risk.table.title="Number at Risk", risk.table.y.text=FALSE,
risk.table.y.text.col=TRUE, risk.table.height = 0.4, xlab="Years Since
Surveillance Scan", ylab="Freedom From\n'Aneurysm Related'\nSecondary
Intervention", surv.scale="percent", legend.title = "Key: ", xlim =
c(0, x), ylim=c(0.85,1), pval.coord = c(0.1, 0.95))
```

```
dev.off()
#HR data
models <-
with(data=DATA1_MI1,exp=coxph(Surv(follow_up_time,aneurysm)~migration_
factor1))
pool_models <- pool(models)
summary<- summary(pool_models)
exp(summary$estimate)#Hazard Ratio
exp(summary$estimate-(1.93*summary$std.error))#Lower 95% CI
exp(summary$estimate+(1.93*summary$std.error))#Upper 95% CI
summary$p.value# p Value
#Hazard Ratio of 4.57 (1.44 - 14.52) p=0.01

########Rationalise flow related variables
DATA2 <- na.omit(DATA1[,c(1:36,40:43)])
DATA2 <-DATA2[order(-DATA2$flow),]
##Full Model
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,flow)~cdus_undiag
nostic+cdus_undiagnostic_cumulative+cdus_limbs+cdus_limbs_cumulative+c
dus_aaa_size+cdus_max_growth+cdus_recent_growth+cdus_recent_growth_rat
e+axr_limb_kink+axr_limb_kink_cumulative)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 741
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,flow)~cdus_undiagnost
ic+cdus_undiagnostic_cumulative+cdus_limbs+cdus_limbs_cumulative+cdus_
aaa_size+cdus_max_growth+cdus_recent_growth+cdus_recent_growth_rate+ax
r_limb_kink+axr_limb_kink_cumulative))
pool_models <- pool(models)
summary<- summary(pool_models)
a<- as.data.frame(summary)
a$hr <- exp(a$estimate)
a$lci <-exp(a$estimate-(1.93*a$std.error))#Lower 95% CI
a$uci <-exp(a$estimate+(1.93*a$std.error))#Upper 95% CI
a
#####. Manually calculating linear predictor
lpdata <-
DATA2[,which(names(DATA2)%in%c("cdus_undiagnostic","cdus_undiagnostic_
cumulative","cdus_limbs","cdus_limbs_cumulative","cdus_aaa_size","cdus
_max_growth","cdus_recent_growth","cdus_recent_growth_rate","axr_limb_
kink","axr_limb_kink_cumulative"))]
lpmat <- model.matrix(~.,data=lpdata)[,-1]
lp.null <- a$estimate%*%t(lpmat)
null.roc<- roc(DATA2$flow,a$estimate%*%t(lpmat))
auc(null.roc)
#####

##Create simplfied model##
#drop CDUS cumulative limbs
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,flow)~cdus_undiag
nostic+cdus_undiagnostic_cumulative+cdus_limbs+cdus_aaa_size+cdus_max_
growth+cdus_recent_growth+cdus_recent_growth_rate+axr_limb_kink+axr_li
mb_kink_cumulative)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 738
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,flow)~cdus_undiagnost
ic+cdus_undiagnostic_cumulative+cdus_limbs+cdus_aaa_size+cdus_max_grow
```

```
th+cdus_recent_growth+cdus_recent_growth_rate+axr_limb_kink+axr_limb_k
ink_cumulative))
pool_models <- pool(models)
summary<- summary(pool_models)
a<- as.data.frame(summary)
a$hr <- exp(a$estimate)
a
#drop CDUS diagnostic cumulative
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,flow)~cdus_undiag
nostic+cdus_limbs+cdus_aaa_size+cdus_max_growth+cdus_recent_growth+cdu
s_recent_growth_rate+axr_limb_kink+axr_limb_kink_cumulative)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 741
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,flow)~cdus_undiagnost
ic+cdus_limbs+cdus_aaa_size+cdus_max_growth+cdus_recent_growth+cdus_re
cent_growth_rate+axr_limb_kink+axr_limb_kink_cumulative))
pool_models <- pool(models)
summary<- summary(pool_models)
a<- as.data.frame(summary)
a$hr <- exp(a$estimate)
a
#drop AXR limb kink cumulative
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,flow)~cdus_undiag
nostic+cdus_limbs+cdus_aaa_size+cdus_max_growth+cdus_recent_growth+cdu
s_recent_growth_rate+axr_limb_kink)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 741
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,flow)~cdus_undiagnost
ic+cdus_limbs+cdus_aaa_size+cdus_max_growth+cdus_recent_growth+cdus_re
cent_growth_rate+axr_limb_kink))
pool_models <- pool(models)
summary<- summary(pool_models)
a<- as.data.frame(summary)
a$hr <- exp(a$estimate)
a
#remove recent growth rate
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,flow)~cdus_undiag
nostic+cdus_limbs+cdus_aaa_size+cdus_max_growth+cdus_recent_growth+axr
_limb_kink)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 741
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,flow)~cdus_undiagnost
ic+cdus_limbs+cdus_aaa_size+cdus_max_growth+cdus_recent_growth+axr_lim
b_kink))
pool_models <- pool(models)
summary<- summary(pool_models)
a<- as.data.frame(summary)
a$hr <- exp(a$estimate)
a
#remove CDUS undiagnostic
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,flow)~cdus_limbs+
cdus_aaa_size+cdus_max_growth+cdus_recent_growth+axr_limb_kink)))
aic <- as.data.frame(models_aic$analyses)[1,]
```

```
aic <- sum(aic)/500
aic # AIC 740
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,flow)~cdus_limbs+cdus
_aaa_size+cdus_max_growth+cdus_recent_growth+axr_limb_kink))
pool_models <- pool(models)
summary<- summary(pool_models)
a<- as.data.frame(summary)
a$hr <- exp(a$estimate)
a
#remove CDUS max growth
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,flow)~cdus_limbs+
cdus_aaa_size+cdus_recent_growth+axr_limb_kink)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 753
#add back CDUS max growth, remove cdus recent growth
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,flow)~cdus_limbs+
cdus_aaa_size+cdus_max_growth+axr_limb_kink)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 747
#add back CDUS recent growth, remove CDUS aaa size
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,flow)~cdus_limbs+
cdus_max_growth+cdus_recent_growth+axr_limb_kink)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 742
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,flow)~cdus_limbs+cdus
_max_growth+cdus_recent_growth+axr_limb_kink))
pool_models <- pool(models)
summary<- summary(pool_models)
a<- as.data.frame(summary)
a$hr <- exp(a$estimate)
a
#remove CDUS recent growth
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,flow)~cdus_limbs+
cdus_max_growth+axr_limb_kink)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 750
#add back CDUS recent growth, remove CDUS max growth
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,flow)~cdus_limbs+
cdus_recent_growth+axr_limb_kink)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 753
#add back CDUS max growth
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,flow)~cdus_limbs+
cdus_max_growth+cdus_recent_growth+axr_limb_kink)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 742
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,flow)~cdus_limbs+cdus
_max_growth+cdus_recent_growth+axr_limb_kink))
```

```
pool_models <- pool(models)
summary<- summary(pool_models)
a<- as.data.frame(summary)
a$hr <- exp(a$estimate)
a$lci <- exp(a$estimate-(1.93*a$std.error))#Lower 95% CI
a$uci <- exp(a$estimate+(1.93*a$std.error))#Upper 95% CI
a
#remove CDUS max growth or CDUS recent growth leads to large increase
in AIC

##Final Simplfied flow model###
#####. Manually calculating linear predictor
lpdata <-
DATA2[,which(names(DATA2)%in%c("cdus_limbs","cdus_max_growth","cdus_re
cent_growth","axr_limb_kink"))]
lpmat <- model.matrix(~.,data=lpdata)[,-1]
lp.simp <- a$estimate%*%t(lpmat)
simp.roc<-roc(DATA2$flow,lp.simp)
auc(simp.roc)
#####
#####
Cairo(file="flow_models_rocs.png", type="png",units="mm", width= 140,
height=70, dpi=600, ponitsize="1")
par(mfrow=c(1,2))
plot(null.roc,main="Full Model",xlim=c(1,0), ylim=c(0,1))
mtext("AUC = 0.95", side=1)
plot(simp.roc,main="Simplified Model",xlim=c(1,0), ylim=c(0,1))
mtext("AUC = 0.95", side=1)
dev.off()
Cairo(file="flow_models_comparison.png", type="png",units="mm", width=
140, height=140, dpi=600, ponitsize="1")
plot(lp.simp,lp.null,col=DATA2$flow+1, pch=3, cex=0.25, xlim=c(-
10,5),ylim=c(-10,5), xlab="Simplified Model", ylab="Full Model")
abline(h=0,lty=2, col="#CCCCCC")
abline(v=0,lty=2, col="#CCCCCC")
dev.off()
lin.mod <- lm(c(lp.simp)~c(lp.null))
summary(lin.mod) ### slope of linear model is close to 1 although
there is some shift (-0.57) actually looking to improve diagnostic
performance


#####################################################

DATA2 <-DATA2[order(-DATA2$aneurysm),]
##Rationalise aneurysm related variables
##Full Model (any endoleak droped to prevent confounding with Type II
And GR enoleak findings)
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,aneurysm)~cdus_un
diagnostic+cdus_gru_endoleak+cdus_t2_endoleak+cdus_aaa_size+cdus_max_g
rowth+cdus_recent_growth+cdus_recent_growth_rate+migration_factor1+axr
_effacement+axr_structural)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 515
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,aneurysm)~cdus_undiag
nostic+cdus_gru_endoleak+cdus_t2_endoleak+cdus_aaa_size+cdus_max_growt
h+cdus_recent_growth+cdus_recent_growth_rate+migration_factor1+axr_eff
acement+axr_structural))
pool_models <- pool(models)
summary<- summary(pool_models)
```

```
a<- as.data.frame(summary)
a$hr <- exp(a$estimate)
a$hr <- exp(a$estimate)
a$lci <- exp(a$estimate-(1.93*a$std.error))#Lower 95% CI
a$uci <- exp(a$estimate+(1.93*a$std.error))#Upper 95% CI
format(a, scientific=F)
#####. Manually calculating linear predictor
lpdata <-
DATA2[,which(names(DATA2)%in%c("cdus_undiagnostic","cdus_gru_endoleak"
,"cdus_t2_endoleak","cdus_aaa_size","cdus_max_growth","cdus_recent_gro
wth","cdus_recent_growth_rate","migration_factor1","axr_effacement","a
xr_structural"))]
lpmat <- model.matrix(~.,data=lpdata)[,-1]
lp.null <- a$estimate%*%t(lpmat)
null.roc<- roc(DATA2$aneurysm,a$estimate%*%t(lpmat))
#####

#backwards stepwise regression
# drop undiagnostic
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,aneurysm)~cdus_gr
u_endoleak+cdus_t2_endoleak+cdus_aaa_size+cdus_max_growth+cdus_recent_
growth+cdus_recent_growth_rate+migration_factor1+axr_effacement+axr_st
ructural)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 513
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,aneurysm)~cdus_gru_en
doleak+cdus_t2_endoleak+cdus_aaa_size+cdus_max_growth+cdus_recent_grow
th+cdus_recent_growth_rate+migration_factor1+axr_effacement+axr_struct
ural))
pool_models <- pool(models)
summary<- summary(pool_models)
a<- as.data.frame(summary)
a$hr <- exp(a$estimate)
format(a, scientific=F)

# drop recent growth rate
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,aneurysm)~cdus_gr
u_endoleak+cdus_t2_endoleak+cdus_aaa_size+cdus_max_growth+cdus_recent_
growth+migration_factor1+axr_effacement+axr_structural)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 529
#add back growth rate remove axr structural
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,aneurysm)~cdus_gr
u_endoleak+cdus_t2_endoleak+cdus_aaa_size+cdus_max_growth+cdus_recent_
growth+cdus_recent_growth_rate+migration_factor1+axr_effacement)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 515
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,aneurysm)~cdus_gru_en
doleak+cdus_t2_endoleak+cdus_aaa_size+cdus_max_growth+cdus_recent_grow
th+cdus_recent_growth_rate+migration_factor1+axr_effacement))
pool_models <- pool(models)
summary<- summary(pool_models)
a<- as.data.frame(summary)
a$hr <- exp(a$estimate)
format(a, scientific=F)
```

```
#trial remove t2 endoleak - ot kept
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,aneurysm)~cdus_gr
u_endoleak+cdus_aaa_size+cdus_max_growth+cdus_recent_growth+cdus_recen
t_growth_rate+migration_factor1+axr_effacement)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 519

#remove aa size
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,aneurysm)~cdus_gr
u_endoleak+cdus_t2_endoleak+cdus_max_growth+cdus_recent_growth+cdus_re
cent_growth_rate+migration_factor1+axr_effacement)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 517
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,aneurysm)~cdus_gru_en
doleak+cdus_t2_endoleak+cdus_max_growth+cdus_recent_growth+cdus_recent
_growth_rate+migration_factor1+axr_effacement))
pool_models <- pool(models)
summary<- summary(pool_models)
a<- as.data.frame(summary)
a$hr <- exp(a$estimate)
format(a, scientific=F)

# remove migration factor
models_aic <-
with(data=DATA1_MI,exp=AIC(coxph(Surv(follow_up_time,aneurysm)~cdus_gr
u_endoleak+cdus_t2_endoleak+cdus_max_growth+cdus_recent_growth+cdus_re
cent_growth_rate+axr_effacement)))
aic <- as.data.frame(models_aic$analyses)[1,]
aic <- sum(aic)/500
aic # AIC 516
models <-
with(data=DATA1_MI,exp=coxph(Surv(follow_up_time,aneurysm)~cdus_gru_en
doleak+cdus_t2_endoleak+cdus_max_growth+cdus_recent_growth+cdus_recent
_growth_rate+axr_effacement))
pool_models <- pool(models)
summary<- summary(pool_models)
a<- as.data.frame(summary)
a$hr <- exp(a$estimate)
a$hr <- exp(a$estimate)
a$lci <- exp(a$estimate-(1.93*a$std.error))#Lower 95% CI
a$uci <- exp(a$estimate+(1.93*a$std.error))#Upper 95% CI
format(a, scientific=F)
#removal of any remaing factor results in AIC gain.  Add in any
removed factor does not result in significant AIC fall.

##Final Simplfied flow model###
#####. Manually calculating linear predictor
lpdata <-
DATA2[,which(names(DATA2)%in%c("cdus_gru_endoleak","cdus_t2_endoleak",
"cdus_max_growth","cdus_recent_growth","cdus_recent_growth_rate","axr_
effacement"))]
lpmat <- model.matrix(~.,data=lpdata)[,-1]
lp.simp <- a$estimate%*%t(lpmat)
simp.roc<-roc(DATA2$aneurysm,lp.simp)
#####
#####
```

```
Cairo(file="aneurysm_models_rocs.png", type="png",units="mm", width=
140, height=70, dpi=600, ponitsize="1")
par(mfrow=c(1,2))
plot(null.roc,main="Full Model",xlim=c(1,0), ylim=c(0,1))
mtext("AUC = 0.92", side=1)
plot(simp.roc,main="Simplified Model",xlim=c(1,0), ylim=c(0,1))
mtext("AUC = 0.91", side=1)
dev.off()
Cairo(file="aneurysm_models_comparison.png", type="png",units="mm",
width= 140, height=140, dpi=600, ponitsize="1")
plot(lp.simp,lp.null, pch=3, cex=0.25, xlab="Simplified Model",
ylab="Full Model")
abline(h=0,lty=2, col="#CCCCCC")
abline(v=0,lty=2, col="#CCCCCC")
dev.off()
lin.mod <- lm(c(lp.simp)~c(lp.null))
summary(lin.mod) ### slope of linear model is 0.83 although there is
some shift (-0.81) actually looking to improve diagnostic performance

################################

#####develop predictive model####
##Dr Richard Jackson's Code###
library(ResourceSelection)
library(DescTools)

#data <- DATA
#save (data,file="data.Rdata")
load (file="data.Rdata")
#Summary of data follow-up
survfit(with(data, Surv(follow_up_time,event))~1) # Number of events
summary(data$follow_up_time) # Follow-up time
#dividing data
data$int <- cut(data$time_since_op,c(0,0.5,1,2,3,4,5,7.5,10,20))
tab <- table(data$int,data$event)
round(tab[,2]/rowSums(tab),2)
data$dum <- substr(data$int,2,2)

data$off <- log(data$time_since_op-as.numeric(data$dum)+1)

### Centering Size & Age
median(DATA$size,na.rm=T)
data$pt_max_preop_AAA_size <- data$pt_max_preop_AAA_size-
mean(data$pt_max_preop_AAA_size[-
which(is.na(data$pt_max_preop_AAA_size))])
data$cdus_aaa_size <- data$cdus_aaa_size-mean(data$cdus_aaa_size[-
which(is.na(data$cdus_aaa_size))])
data$pt_age_at_operation <- data$pt_age_at_operation-
mean(data$pt_age_at_operation)
data$cdus_recent_growth <- data$cdus_recent_growth-
mean(data$cdus_recent_growth)mean(data$cdus_recent_growth[-
which(is.na(data$cdus_recent_growth))])

### Model
pois.mod <- glm(event~-1+int+pt_max_preop_AAA_size+cdus_aaa_size+
pt_age_at_operation
+cdus_any_endoleak,family="poisson",data=data,offset=off)
AIC(pois.mod)
anova(pois.mod,test="Chisq")
summary(pois.mod)

### Measures of Discrimination
cs <- Cstat(pois.mod)
```

```
### Measures of Calibration
hl <- hoslem.test(as.numeric(pois.mod$y),fitted(pois.mod))


### AUC
pred <- prediction(fitted(pois.mod),as.numeric(pois.mod$y))
auc <- attributes(performance(pred,"auc"))$"y.values"[[1]]

plot(performance(pred,"sens","fpr"),col=4,lwd=3)
abline(a=0,b=1,lty=2,lwd=2)

summ <- c(cs,hl$p.value,auc)


##### Function model

## Wrapping the model up in a function makes it easier for
bootstrapping

model <- function(data){

  ### Model
  pois.mod <- glm(event~-1+int+pt_max_preop_AAA_size+cdus_aaa_size+
pt_age_at_operation
+cdus_any_endoleak,family="poisson",data=data,offset=off)
  AIC(pois.mod)
  anova(pois.mod,test="Chisq")
  summary(pois.mod)


  ### Measures of Discrimination
  cs <- Cstat(pois.mod)

  ### Measures of Calibration
  ## Hoslem
  #hlt <- hoslem.test(as.numeric(valid$event[-miss.id]),exp(pr[-
miss.id]),g=10)

  #x2 <- sum((hlt$observed[,1]-hlt$expected[,1])^2/hlt$expected[,1])
  #hl <- 1-pchisq(x2,2)

  ### AUC
  pred <- prediction(fitted(pois.mod),as.numeric(pois.mod$y))
  auc <- attributes(performance(pred,"auc"))$"y.values"[[1]]

  #plot(performance(pred,"sens","fpr"),col=4,lwd=3)
  #abline(a=0,b=1,lty=2,lwd=2)

  summ <- c(cs,hl,auc)

  ret <- list(pois.mod,summ)
}

### settting up bootstrap
un.pat <- unique(data$pt_id)
n.pat <- length(un.pat)
nboot <- 5000

co <- matrix(NA,nboot,13)
hl <- rep(NA,nboot)
hlob <- matrix(NA,10,nboot)
hlex <- matrix(NA,10,nboot)
```

```
auc <- rep(NA,nboot)
devPerc <- rep(NA,nboot)


for(sim in 1:nboot){

  sample <- sample(n.pat,n.pat*0.2)
  id <- which(data$pt_id%in%un.pat[sample])

  train <- data[-id,]
  valid <- data[id,]

  ### Training model
  mod <- model(train)[[1]]

  ### Getting predictions
  val <-
valid[,which(names(valid)%in%c("int","pt_max_preop_AAA_size","cdus_aaa
_size","pt_age_at_operation","cdus_any_endoleak","off"))]
  pr <- predict(mod,val)
  miss.id <- which(is.na(pr))

  pred <- prediction(pr[-miss.id],valid$event[-miss.id])
  auc[sim] <- attributes(performance(pred,"auc"))$"y.values"[[1]]

  #plot(performance(pred,"sens","fpr"),col=4,lwd=3)
  #abline(a=0,b=1,lty=2,lwd=2)
  #boxplot(pr[-miss.id]~valid$event[-miss.id])


  ## Hoslem
  hlt <- hoslem.test(as.numeric(valid$event[-miss.id]),exp(pr[-
miss.id]),g=10)


  x2 <- sum((hlt$observed[,1]-hlt$expected[,1])^2/hlt$expected[,1])
  hl[sim] <- 1-pchisq(x2,2)

  ### COEF
  co[sim,] <- coef(mod)[]

  #### Percentage of deviance explained
  devPerc[sim] <- 1-mod$deviance/mod$null.deviance
}
auc <- ifelse(auc<0.5,1-auc,auc)

###Save / Load Point###
#save validation data
#save(auc,hl,devPerc,co, file ="model.Rdata")
# load validation
load(file="model.Rdata")
###End Save/Load Point###

#Creating model with mean coefficents from internal validation
test <- NA
for(a in 1:13){
  test[a]<- as.double(mean(co[,a]))
}
pois.mod1 <- pois.mod
pois.mod1$coefficients <- test
rm(test)
pois.mod$
##Output from internal validation
```

```
summary(auc)
summary(hl)
summary(devPerc)
summary(pois.mod1)
# Histogram of Model AUC with density plot
Cairo(file="auc_histogram_validation.png", type="png",units="mm",
width= 140, height=100, dpi=600, ponitsize="1")
ggplot()+
  aes(auc) +
  geom_histogram(aes(y=..density..), colour="black", fill="white")+
  geom_density(alpha=.2, fill="#FF6666")+
  scale_x_continuous(breaks = seq(0.5, by = 0.1))+
  xlim (0.5,1)+
  scale_y_continuous(breaks = seq(0, 10, by = 2))+
  xlab("Area Under Curve")+
  ylab("Percentage of Validation Models")
dev.off()
# Histogram of Hosmer-Lemeshow test p value with density plot
Cairo(file="HL-test_histogram_validation.png", type="png",units="mm",
width= 140, height=100, dpi=600, ponitsize="1")
ggplot()+
  aes(hl) +
  geom_histogram(aes(y=..density..), colour="black", fill="white")+
  geom_density(alpha=.2, fill="#FF6666")+
  scale_x_continuous(breaks = seq(0,1, by = 0.1))+
  #geom_vline(aes(xintercept=median(hl)), color="blue",
linetype="dashed", size=1)+
  xlab("p Value of Hosmer-Lemeshow Test")+
  ylab("Percentage of Validation Models")
dev.off()

##Risk Plots for 3 (Low, Mean & High risk) Patients
#Average interval to next scan for cross-section of whole programe
datatest <- data
b <- as.numeric(count(datatest))
datatest$interval <-NA
for(a in 1:b){
  datatest$interval[a] <-
ifelse(datatest$pt_id[a]==datatest$pt_id[a+1],datatest$time_since_op[a
+1]-datatest$time_since_op[a],NA)
}
z<- mean(datatest$interval[!is.na(datatest$interval)])
rm(datatest,b)
#Risk of secondary intervention in that time
x <- summary(survfit(Surv(data$follow_up_time,data$event)~1), times=z)

#Create time matrix
time <-seq(0,20,length=100)
co.mat <- matrix(seq(0,20,length=100),100,9)
co <- coef(pois.mod1)
co.mat[which(co.mat[,1]>0.5),1] <- 0.5
co.mat[which(co.mat[,2]<0.5),2] <- 0
co.mat[which(co.mat[,2]>1),2] <- 1
co.mat[which(co.mat[,3]<1),3] <- 0
co.mat[which(co.mat[,3]>2),3] <- 2
co.mat[which(co.mat[,4]<2),4] <- 0
co.mat[which(co.mat[,4]>3),4] <- 3
co.mat[which(co.mat[,5]<3),5] <- 0
co.mat[which(co.mat[,5]>4),5] <- 4
co.mat[which(co.mat[,6]<4),6] <- 0
co.mat[which(co.mat[,6]>5),6] <- 5
co.mat[which(co.mat[,7]<5),7] <- 0
co.mat[which(co.mat[,7]>7.5),7] <- 7.5
```

```
co.mat[which(co.mat[,8]<7.5),8] <- 0
co.mat[which(co.mat[,8]>10),8] <- 10
co.mat[which(co.mat[,9]<10),9] <- 0
co.mat[,2] <- co.mat[,2]-0.5
co.mat[,3] <- co.mat[,3]-1
co.mat[,4] <- co.mat[,4]-2
co.mat[,5] <- co.mat[,5]-3
co.mat[,6] <- co.mat[,6]-4
co.mat[,7] <- co.mat[,7]-5
co.mat[,8] <- co.mat[,8]-7.5
co.mat[,9] <- co.mat[,9]-10
co.mat[which(co.mat<0)] <- 0
rowSums(co.mat)
#High Risk Patient: Time of CDUS scan after operation = 0.11 years,
Pre-op AAA size = 57mm, Current CDUS size =65mm, Patient age at
operation = 70 years and CDUS Endoleak = TRUE
#Mean Risk Patient:  Time of CDUS scan after operation = 3.16 years,
Pre-op AAA size = 65mm, Current CDUS size =57mm, Patient age at
operation = 75 years and CDUS Endoleak = FALSE
#Low Risk Patient:  Time of CDUS scan after operation = 4.34 years,
Pre-op AAA size = 70mm, Current CDUS size =45mm, Patient age at
operation = 80 years and CDUS Endoleak = FALSE

base <- c(exp(co[1:9])%*%t(co.mat));base
vc <- vcov(pois.mod1)
se <- sqrt(diag(vc[1:9,1:9]))
se2 <- sum(diag(vc[10:13,10:13]))

co.lo <- co[1:9]-1.96*se
co.up <- co[1:9]+1.96*se

base.lo <- c(exp(co.lo[1:9])%*%t(co.mat));base.lo
base.up <- c(exp(co.up[1:9])%*%t(co.mat));base.up

co2 <- co[10:13]
co2.lo <- co2-1.96*se2
co2.up <- co2+1.96*se2

### Hi Iain, I haven't got the exact centering values for age and
pre/post aaa size but i've used 60 for everything - can you cahnge to
be more accurate?
pat1.hr <- c(exp(co2%*%c(57-64.99,65-56.94,70-75.15,1)));pat1.hr
pat1.hr.lo <- c(exp(co2.lo%*%c(57-64.99,65-56.94,70-
75.15,1)));pat1.hr.lo
pat1.hr.up <- c(exp(co2.up%*%c(57-64.99,65-56.94,70-
75.15,1)));pat1.hr.up

pat2.hr <- c(exp(co2%*%c(65-64.99,57-56.94,75-75.15,0)));pat2.hr
pat2.hr.lo <- c(exp(co2.lo%*%c(65-64.99,57-56.94,75-
75.15,0)));pat2.hr.lo
pat2.hr.up <- c(exp(co2.up%*%c(65-64.99,57-56.94,75-
75.15,0)));pat2.hr.up

pat3.hr <- c(exp(co2%*%c(70-64.99,45-56.94,80-75.15,0)));pat3.hr
pat3.hr.lo <- c(exp(co2.lo%*%c(70-64.99,45-56.94,80-
75.15,0)));pat3.hr.lo
pat3.hr.up <- c(exp(co2.up%*%c(70-64.99,45-56.94,80-
75.15,0)));pat3.hr.up

H1 <- 1-exp(-base)^pat1.hr;H1
H1.lo <- 1-exp(-base.lo)^pat1.hr.lo;H1.lo
H1.up <- 1-exp(-base.up)^pat1.hr.up;H1.up
```

```
H2 <- 1-exp(-base)^pat2.hr;H2
H2.lo <- 1-exp(-base.lo)^pat2.hr.lo;H2.lo
H2.up <- 1-exp(-base.up)^pat2.hr.up;H2.up

H3 <- 1-exp(-base)^pat3.hr;H3
H3.lo <- 1-exp(-base.lo)^pat3.hr.lo;H3.lo
H3.up <- 1-exp(-base.up)^pat3.hr.up;H3.up

##Output Plot
png(filename="patient_risk_plots.png", units="mm", width= 140,
height=100, res=600, pointsize="12")
plot(ylab="Cumulative Risk of Secondary Intervention",xlab="Time after
Surveillance Scan (Years)",(time),H1,col=1,typ="l",lwd=2,xlim=c(0,3),
ylim=c(0,0.4))
lines((time),H1.lo,lty=10,lwd=1)
lines((time),H1.up,lwd=1,lty=10)
lines((time),H2,col=2,lwd=2)
lines((time),H2.lo,col=2,lwd=1,lty=10)
lines((time),H2.up,col=2,lwd=1,lty=10)
lines((time),H3,col=3,lwd=2)
lines((time),H3.lo,col=3,lwd=1,lty=10)
lines((time),H3.up,col=3,lwd=1,lty=10)
cbind(time,H1,H1.lo,H1.up,H2,H2.lo,H2.up,H3,H3.lo,H3.up)
abline(h=(1-x$surv),lty=3, col="#505050")
legend(-0.075,0.425,c("High Risk Patient","Mean Risk Patient","Low
Risk Patient"),lwd=2,col=c(1,2,3),bty="n")
dev.off()
```

3. Anonymised Patient Data And Imaging Variables From The LiVES Database

Copies of the following files are on the accompanying CD in the pocket attached to the inside back cover.

CD\database\patient_level_data.csv

CD\database\secondary_interventions.csv

CD\database\all_scans.csv

CD\database\axr_migration_factor.csv

4. Participant Information Leaflet

Participant Information Leaflet

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

Contrast Enhanced Ultrasound in EVAR Surveillance for Endoleak Detection: Compared to Time-Resolved CT Angiography

We invite you to take part in a research study, which is taking place at The Royal Liverpool Hospital.

Before you decide whether to take part, it is important for you to understand what's involved and why the research is being done.

Please read this information carefully & feel free to talk it over with family or friends. If you are unclear about anything please feel free to ask questions or ask for more information.

It's your decision if you wish to take part or not. If you choose not to take part it will not affect the care you receive from your doctors.

Why have I been asked to participate?

Your own medical team have identified you as someone suitable to take part in the study because:

You have previously had an EndoVascular Aneurysm Repair (EVAR), which is often called "stenting" of an aneurysm

&

Your medical team now feel you need to have two types of scans to ensure the stent is working the way it should.

1. A Computerised Tomography (CT) scan.
   X-Rays are taken by a table moving through a scanner, as dye is put through a needle in your arm. You will have had a CT Scan before you had your EVAR operation.

2. A Contrast Enhanced Ultrasound.
   This is a scan that involves a sonographer moving a probe over your tummy with some "jelly" on it. This type of ultrasound also involves an injection in your arm. You may not have had this before.

Why are you doing the research?

We currently use ultrasound (without contrast) as the main scan to check that EVAR stents are working as they should.

We already know that standard CT scans can give us clearer information. However, they carry some risks. They involve x-rays and a dye that can damage the kidneys. So we only use them when we have a concern.

Contrast Enhanced Ultrasound is a promising new scan and may reduce the number of CT scans we need to do.

Previous studies comparing the two types of scan have shown very different results. We want to find out which type of scan gives the best information of how your stent is working.

What is involved in the study?

If you choose to participate in the research study you would be asked to attend the Royal Liverpool Hospital for approximately half a day. During the visit you would;

1. be asked a series of questions about your health
2. have a cannula/tube placed in an arm vein for the scans
3. have a Contrast Enhanced Ultrasound Scan
4. have a special CT scan - which is slightly different to a planned CT Scan.

Researchers would also access your hospital records;

1. to record that you participated in the trial,
2. to look up details of any previous scans you've had
3. to review the results of any other investigations you've had of your heart
4. to see what effect the study scans have on your care.

Is there anything else involved?

No. Once you've had your scans, there is no other time commitment or input required.
The reports of the scans will be made available to your own surgeon who will then decide if you require anything else done and look after you as normal.

How is the CT scan in the research study different?

A 'standard' CT scan has two sets of images of your whole tummy. The first is shortly after the injection of the dye and the second, a minute or two later.
The research CT scan performed in the study has several sets of images

of just the stent, followed by one set of the whole tummy a minute or two later.

This means the table you lie down on during the CT scan will move backwards and forwards several times through the scanner, instead of just twice. Also you will be asked to try and hold your breath for a bit longer than you might otherwise be.

Is it risky to take part?

The study has been designed so that the amount of x-rays from the two different types of CT scans would be similar. It is impossible to say it will be exactly the same.

The scanner calculates the amount of radiation needed based on the shape of your body as it is performing the scan.
Although there are more sets of images taken within the research CT Scan they are of a smaller area and using a lower dose of x-rays, so the overall amount should be roughly the same.

The x-rays used in CT scans are associated with some risk of causing cancer. However this risk is small. The older you are the smaller this risk is.

Your own surgeon/team feel that this risk is justified to ensure your EVAR stent is working properly.

Any other risks to do with the scans are the same if you choose to take part or not. If you wish to discuss these then please ask.

What if I choose not to take part?

If you choose not to take part in the research study, the ‘standard’ scans will be arranged by your own team and the researchers will not have any access to them or to your medical records.

What if something goes wrong?

The risk of you suffering harm as a result of taking part is minimal, and study has insurance in place to provide compensation for any negligent harm caused by taking part.

Who will be told if I take part?

Your GP is the only person outside the hospital who will be informed that you have taken part in the research. If you do not wish your GP to be informed you can tell us this on the consent form.

Will I receive any money for taking part?

No. There is no provision for financial reimbursement, as these scans would be part of your normal care.
Potentially you will save a visit to the hospital as both scans will definitely be done the same day within the study.

Will I find out the results of the research?

Your own clinical team will be able to tell you the results of your scans and what they mean for your care.
If you choose to, we will write to you with the results of the study as a whole once it is completed.

What happens now?

The researcher who gave you, or sent you this leaflet will arrange to contact you again after you have had a chance to read it. Please feel free to ask them as many questions as you wish.
If you wish to take part in the research study then they will arrange a time for you to come to the hospital.

If you don't wish to take part in the research study then they will let your doctor know to arrange the scans in the normal way.

What if I have questions?

Please ask us if there is anything you would like clarified.
If you'd like to look something up your-self http://www.nhs.uk/ is a good source of information if you're unsure of anything described in this leaflet. Simple use the search feature in the top right corner.

What if I have a complaint about the study?

If you wish to make a complaint regarding the study this can be made to Prof Vallabhaneni (details below). If you would prefer someone independent you can discuss your concerns with the Patient advice and liaison services (PALS).

PALS Tel: 0151 706 4903

PALS
The Royal Liverpool University Hospital
Prescot Street
Liverpool
L7 8XP

How to contact us?

If you have any questions please contact the doctors who are organising the study;

Prof Vallabhanenior Mr Iain Roy,
Tel: 0151 706 3457
e-mail: iain.roy@rlbuht.nhs.uk

Link 8c
The Royal Liverpool University Hospital
Prescot Street
Liverpool
L7 8XP

5. Data Collection Pro-forma

Participant Study ID:

Participant Questionnaire:

Reason for further investigation:

Height (cm):
Weight (kg):
Blood Pressure:
Pulse rate:

Functional Status:
0 - you are fully active, more or less as you were before your illness

1 - you cannot carry out heavy physical work, but can do anything else

2 - you are up and about more than half the day. You can look after yourself, but cannot work

Estimated walking distance:

Previous Heart Disease:
Known to have AF or other arythmia: Yes/No
Known IHD (Angina, ACS, MI): Yes/No Details:……
Previous Treatments:

Patients had echo in past: Yes/No Details……..

Current Medications:

CDU:

Participant Study ID:
Completed by (investigators name):
Time start: Time Completed:

Diagnostic images obtained of:

Aortic neck	Yes/No		
Aneurysm body with graft in situ	Yes/No		
Bifurcation	Yes/No		
Right CIA (Midpoint of limb)	Yes/No	Left CIA (Midpoint of limb)	Yes/No
Right Limb/native transition	Yes/No	Left Limb/native transition	Yes/No

Aortic Measurements:
PSV in native aorta:
Native Aorta PI:
Neck / D2 diameter (mm):
Aneurysm /D3 diameter (mm):

Endoleak seen: Yes/No

Details:	Endoleak 1	Endoleak 2	Endoleak 3
Type:	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other
Inflow point(s):			
Outflow point(s):			
Certain of flow direction:	Yes/No	Yes/No	Yes/No

Limbs:

	Right	Left
Distal PSV measurement		
PI		
Wave form	Mono / Bi / Triphasic	Mono / Bi / Triphasic

Comments:

Common Femoral Arteries:

	Right	Left
Distal PSV measurement		
PI		
Wave form	Mono / Bi / Triphasic	Mono / Bi / Triphasic

Comments:

CEUS:

Participant Study ID:
Completed by (investigators name):
Time start: Time Completed:

First Contrast Injection: (all timings from start of contrast injection)

Time till seen in graft(s):
Time till seen in endoleak (s):

Contrast seen in Endoleak 1:	Yes / No	Endoleak 1 Type: Ia/Ib/II/III/Other
Contrast Seen in Endoleak 2:	Yes / No	Endoleak 2 Type: Ia/Ib/II/III/Other
Contrast seen in Endoleak 3:	Yes / No	Endoleak 3 Type: Ia/Ib/II/III/Other

Second Contrast Injection:

Time till seen in graft(s):
Time till seen in endoleak (s):

Contrast seen in Endoleak 1:	Yes / No	Endoleak 1 Type: Ia/Ib/II/III/Other
Contrast Seen in Endoleak 2:	Yes / No	Endoleak 2 Type: Ia/Ib/II/III/Other
Contrast seen in Endoleak 3:	Yes / No	Endoleak 3 Type: Ia/Ib/II/III/Other

Temporal CTA (in scan measurements)

Participant Study ID: Completed by (investigators name):

Time start: Time Completed:

Temporal CTA (reporting)

Completed by (investigators name):

Time reporting started: Time reporting finished:

Phase 2.5 Seconds

Image quality: Fully diagnostic 5 4 3 2 1 Non-diagnostic

Endoleak seen: Yes/No

Details:	Endoleak 1	Endoleak 2	Endoleak 3
Type:	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other
Inflow point(s):			
HU at inflow:			
Outflow point(s):			
HU at outflow:			
Certain of flow direction:	Yes/No	Yes/No	Yes/No

Hounsfield Unit measurements: (excluding any calcification of graft structures)

Inferior vena cava: ..... HU

Aortic lumen at superior fabric markers of endograft: ..... HU

Aortic lumen at bifurcation of endograft: ..... HU

Iliac lumen at Distal end of right limb of endograft ..... HU

Iliac lumen at distal end of left limb of endograft ..... HU

Phase 5 Seconds

Image quality: Fully diagnostic 5 4 3 2 1 Non-diagnostic

Endoleak seen: Yes/No

Details:	Endoleak 1	Endoleak 2	Endoleak 3
Type:	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other
Inflow point(s):			
HU at inflow:			
Outflow point(s):			
HU at outflow:			
Certain of flow direction:	Yes/No	Yes/No	Yes/No

Hounsfield Unit measurements: (excluding any calcification of graft structures)

Inferior vena cava: ..... HU

Aortic lumen at superior fabric markers of endograft: ..... HU

Aortic lumen at bifurcation of endograft: ..... HU

Iliac lumen at Distal end of right limb of endograft ..... HU

Iliac lumen at distal end of left limb of endograft ..... HU

Phase 7.5 Seconds

Image quality: Fully diagnostic 5 4 3 2 1 Non-diagnostic

Endoleak seen: Yes/No

Details:	Endoleak 1	Endoleak 2	Endoleak 3
Type:	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other
Inflow point(s):			
HU at inflow:			
Outflow point(s):			
HU at outflow:			
Certain of flow direction:	Yes/No	Yes/No	Yes/No

Hounsfield Unit measurements: (excluding any calcification of graft structures)

Inferior vena cava: ……. HU
Aortic lumen at superior fabric markers of endograft: ……. HU
Aortic lumen at bifurcation of endograft: ……. HU
Iliac lumen at Distal end of right limb of endograft ……. HU
Iliac lumen at distal end of left limb of endograft ……. HU

Phase 10 Seconds

Image quality: Fully diagnostic 5 4 3 2 1 Non-diagnostic

Endoleak seen: Yes/No

Details:	Endoleak 1	Endoleak 2	Endoleak 3
Type:	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other
Inflow point(s):			
HU at inflow:			
Outflow point(s):			
HU at outflow:			
Certain of flow direction:	Yes/No	Yes/No	Yes/No

Hounsfield Unit measurements: (excluding any calcification of graft structures)

Inferior vena cava: ……. HU
Aortic lumen at superior fabric markers of endograft: ……. HU
Aortic lumen at bifurcation of endograft: ……. HU
Iliac lumen at Distal end of right limb of endograft ……. HU
Iliac lumen at distal end of left limb of endograft ……. HU

Phase 15 Seconds

Image quality: Fully diagnostic 5 4 3 2 1 Non-diagnostic

Endoleak seen: Yes/No

Details:	Endoleak 1	Endoleak 2	Endoleak 3
Type:	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other
Inflow point(s):			
HU at inflow:			
Outflow point(s):			
HU at outflow:			
Certain of flow direction:	Yes/No	Yes/No	Yes/No

Hounsfield Unit measurements: (excluding any calcification of graft structures)

Inferior vena cava: ……. HU
Aortic lumen at superior fabric markers of endograft: ……. HU
Aortic lumen at bifurcation of endograft: ……. HU
Iliac lumen at Distal end of right limb of endograft ……. HU
Iliac lumen at distal end of left limb of endograft ……. HU

Phase 20 Seconds

Image quality: Fully diagnostic 5 4 3 2 1 Non-diagnostic

Endoleak seen: Yes/No

Details:	Endoleak 1	Endoleak 2	Endoleak 3
Type:	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other
Inflow point(s):			
HU at inflow:			
Outflow point(s):			
HU at outflow:			
Certain of flow direction:	Yes/No	Yes/No	Yes/No

Hounsfield Unit measurements: (excluding any calcification of graft structures)

Inferior vena cava: ……. HU
Aortic lumen at superior fabric markers of endograft: ……. HU
Aortic lumen at bifurcation of endograft: ……. HU
Iliac lumen at Distal end of right limb of endograft ……. HU
Iliac lumen at distal end of left limb of endograft ……. HU

Phase 25 Seconds

Image quality: Fully diagnostic 5 4 3 2 1 Non-diagnostic

Endoleak seen: Yes/No

Details:	Endoleak 1	Endoleak 2	Endoleak 3
Type:	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other
Inflow point(s):			
HU at inflow:			
Outflow point(s):			
HU at outflow:			
Certain of flow direction:	Yes/No	Yes/No	Yes/No

Hounsfield Unit measurements: (excluding any calcification of graft structures)

Inferior vena cava: ……. HU
Aortic lumen at superior fabric markers of endograft: ……. HU
Aortic lumen at bifurcation of endograft: ……. HU
Iliac lumen at Distal end of right limb of endograft ……. HU
Iliac lumen at distal end of left limb of endograft ……. HU

Venous Phase

Image quality: Fully diagnostic 5 4 3 2 1 Non-diagnostic

Endoleak seen: Yes/No

Details:	Endoleak 1	Endoleak 2	Endoleak 3
Type:	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other	Ia/Ib/II/III/Other
Inflow point(s):			
HU at inflow:			
Outflow point(s):			
HU at outflow:			
Certain of flow direction:	Yes/No	Yes/No	Yes/No

Hounsfield Unit measurements: (excluding any calcification of graft structures)

Inferior vena cava: ……. HU
Aortic lumen at superior fabric markers of endograft: ……. HU
Aortic lumen at bifurcation of endograft: ……. HU
Iliac lumen at Distal end of right limb of endograft ……. HU
Iliac lumen at distal end of left limb of endograft ……. HU

Other comments / diagnostic findings:

6. R Code to Process Prospective Study

A copy of this code is also available on the accompanying CD in the pocket attached to the inside back cover

CD\ceus_tcta\final_data_analysis.R

```
# Code Created by Iain N Roy, Institute of Ageing & Chronic Disease,
University of Liverpool
# Contact via iainroy@liverpool.ac.uk
# Code to process data for:
# Study Title "Contrast Enhanced Ultrasound Endoleak Detection
Compared To Time-Resolved Computer Tomography Angiography in high risk
Endovascular Aneurysm Repair (EVAR) surveillance patients.
# Study Ethical approval: NHS REC reference: 15/NW/0908
# Code shared as part of the publication under a CCBY

# Code created in R Studio v1.1.463 using R version 3.5.2

# The studies final data (final_data.xlsx) is assumed to be in the
working directory for this R script

# Loading Required Packages
install.packages(c("readxl", "DTComPair", "ggplot2", "ggpubr","egg"))
library(readxl)
library(DTComPair)
library(ggplot2)
library(ggpubr)
library(egg)
library(MASS)
library(dplyr)

# Load Data
demographics <- read_excel("final_data.xlsx", sheet = 1,
col_names=TRUE,
col_types=c("numeric","text","numeric","numeric","numeric","numeric","
numeric","numeric","numeric","logical","logical",
"numeric","numeric","text"), na=c("NA"))
cdus <- read_excel("final_data.xlsx", sheet = 2, col_names=TRUE,
col_types=c("numeric",
"text","text","logical","logical","logical","logical","logical","logic
al","numeric","numeric","numeric","text","numeric","logical","logical"
,"logical","text","text","text","text","text","text","numeric","numeri
c","text","numeric","numeric","text","numeric","numeric","text","numer
ic","numeric","text","text","text","text","text"),na=c("NA"))
ceus <- read_excel("final_data.xlsx", sheet = 3)
tcta <- read_excel("final_data.xlsx", sheet = 4)
final <- read_excel("final_data.xlsx", sheet = 5)
tcta_monitoring <- read_excel("final_data.xlsx", sheet = 6)
tcta_enhhancement <- read_excel("final_data.xlsx", sheet = 7)
tcta_radiation <- read_excel("final_data.xlsx", sheet = 8)
tcta_addition_enhacement_data <- read_excel("final_data.xlsx", sheet =
9)
tcta_ceus_timings <- read_excel("ceus_tcta_el_timings.xlsx")

#Data Catagorisation
#Demographics
demographics$`Sex (Male / Female)` <- as.factor(demographics$`Sex
(Male / Female)`)
demographics$`Height (m)` <- as.numeric(demographics$`Height (m)`)
demographics$`Weight (Kg)` <- as.numeric(demographics$`Weight (Kg)`)
```

```
demographics$`Estimated Walking Distance (m)` <-
as.integer(demographics$`Estimated Walking Distance (m)`)
demographics$`Known Ischemic Heart Disease (True / False)` <-
as.logical(demographics$`Known Ischemic Heart Disease (True / False)`)
demographics$`Known Arythmia (True / False)` <-
as.logical(demographics$`Known Arythmia (True / False)`)
demographics$`Functional Status (add clasification)` <-
as.factor(demographics$`Functional Status (add clasification)`)
demographics$Graft <- as.factor(demographics$Graft)
#CEUS
ceus$`CEUS Graft-Related Endoleak (True/False)`<-
as.integer(as.logical(ceus$`CEUS Graft-Related Endoleak
(True/False)`))
ceus$`CEUS Any Endoleak  (True/False)`<-
as.integer(as.logical(ceus$`CEUS Any Endoleak  (True/False)`))
ceus$`CEUS Type II Endoleak (True / False)`<-
as.integer(as.logical(ceus$`CEUS Type II Endoleak (True / False)`))
#tCTA
tcta$`tCTA Graft-Related Endoelak (True/False)`<-
as.integer(as.logical(tcta$`tCTA Graft-Related Endoelak
(True/False)`))
tcta$`tCTA Any Endoleak (True / False)` <-
as.integer(as.logical(tcta$`tCTA Any Endoleak (True / False)`))
tcta$`tCTA Type II Endoleak (True / False)`<-
as.integer(as.logical(tcta$`tCTA Type II Endoleak (True / False)`))
#final
final$`Any Endoleak (TRUE / FALSE)` <-
as.integer(as.logical(final$`Any Endoleak (TRUE / FALSE)`))
final$`Graft Related Endoleak (TRUE / FALSE)` <-
as.integer(as.logical(final$`Graft Related Endoleak (TRUE / FALSE)`))
final$`Type II Endoleak (TRUE / FALSE)` <-
as.integer(as.logical(final$`Type II Endoleak (TRUE / FALSE)`))
#tCTA Enhancment Data
tcta_enhhancement$`Participant ID` <-
as.numeric(tcta_enhhancement$`Participant ID`)
tcta_enhhancement$`Phase (s)` <- as.numeric(tcta_enhhancement$`Phase
(s)`)
tcta_enhhancement$`Enhancement (HU)` <-
as.numeric(tcta_enhhancement$`Enhancement (HU)`)
tcta_enhhancement$Measurement <-
as.factor(tcta_enhhancement$Measurement)
tcta_enhhancement$`Measurement Class` <-
as.factor(tcta_enhhancement$`Measurement Class`)
tcta_enhhancement <-
tcta_enhhancement[!(is.na(tcta_enhhancement$Measurement)),]
tcta_enhhancement <-
tcta_enhhancement[!tcta_enhhancement$Measurement=="Left Limb",]
tcta_enhhancement <-
tcta_enhhancement[!tcta_enhhancement$Measurement=="Right Limb",]

tcta_addition_enhacement_data$`Participant ID` <-
as.factor(tcta_addition_enhacement_data$`Participant ID`)
tcta_addition_enhacement_data$`Phase (s)` <-
as.numeric(tcta_addition_enhacement_data$`Phase (s)`)
tcta_addition_enhacement_data$`Enhancement (HU)` <-
as.numeric(tcta_addition_enhacement_data$`Enhancement (HU)`)
tcta_addition_enhacement_data$Measurement <-
as.factor(tcta_addition_enhacement_data$Measurement)
tcta_addition_enhacement_data$`Measurement Class` <-
as.factor(tcta_addition_enhacement_data$`Measurement Class`)
tcta_addition_enhacement_data <-
tcta_addition_enhacement_data[!(is.na(tcta_addition_enhacement_data$Me
asurement)),]
```

```
tcta_addition_enhacement_data <-
tcta_addition_enhacement_data[!tcta_addition_enhacement_data$Measureme
nt=="Left Limb",]
tcta_addition_enhacement_data <-
tcta_addition_enhacement_data[!tcta_addition_enhacement_data$Measureme
nt=="Right Limb",]

tcta_monitoring$`tCTA Time For Monitoring to Trigger i.e. >90HU (s)`
<- as.numeric(tcta_monitoring$`tCTA Time For Monitoring to Trigger
i.e. >90HU (s)`)


# Data Processing
demographics$bmi <- as.numeric(demographics$`Weight
(Kg)`/(demographics$`Height (m)`*demographics$`Height (m)`))

# Creating data frames for diagnostic value analysis
ceusvtcta <- merge(ceus,tcta, by= "Participant ID")
ceusvtctavfinal <-merge(ceusvtcta,final,by= "Participant ID")

GREL_tab <-tab.1test(d=ceusvtcta$`tCTA Graft-Related Endoelak
(True/False)`,y=ceusvtcta$`CEUS Graft-Related Endoleak (True/False)`)
ANYEL_tab <-tab.1test(d=ceusvtcta$`tCTA Any Endoleak (True /
False)`,y=ceusvtcta$`CEUS Any Endoleak  (True/False)`)
T2EL_tab <-tab.1test(d=ceusvtcta$`tCTA Type II Endoleak (True /
False)`,y=ceusvtcta$`CEUS Type II Endoleak (True / False)`)

GRELFD_tab <- tab.paired(d=ceusvtctavfinal$`Graft Related Endoleak
(TRUE / FALSE)`, y1=ceusvtctavfinal$`tCTA Graft-Related Endoelak
(True/False)`,y2=ceusvtctavfinal$`CEUS Graft-Related Endoleak
(True/False)`)
ANYELFD_tab <- tab.paired(d=ceusvtctavfinal$`Any Endoleak (TRUE /
FALSE)`, y1=ceusvtctavfinal$`tCTA Any Endoleak (True / False)`,
y2=ceusvtctavfinal$`CEUS Any Endoleak  (True/False)`)
T2ELFD_tab <- tab.paired(d=ceusvtctavfinal$`Type II Endoleak (TRUE /
FALSE)`, y1=ceusvtctavfinal$`tCTA Type II Endoleak (True / False)`,
y2=ceusvtctavfinal$`CEUS Type II Endoleak (True / False)`)

# Creating dataframe for intial enhancment analysis
a<- data.frame (tcta_monitoring$`Participant ID`,
tcta_monitoring$`tCTA Time For Monitoring to Trigger i.e. >90HU (s)`)
colnames(a) <- c("Participant ID","tCTA Time For Monitoring to Trigger
i.e. >90HU (s)")

all_enhancement_data <- merge (tcta_enhhancement, a, by= "Participant
ID", no.dups=FALSE)
all_enhancement_data$`Participant ID`<-
as.factor(all_enhancement_data$`Participant ID`)
all_enhancement_data$timing <-all_enhancement_data$`Phase (s)` +
all_enhancement_data$`tCTA Time For Monitoring to Trigger i.e. >90HU
(s)`
#all_enhancement_data$timing[all_enhancement_data$timing>=75] <- 75

#creating dataframe for second enhament analysis
tcta_addition_enhacement_data$'tCTA Time For Monitoring to Trigger
i.e. >90HU (s)' <- 0
tcta_addition_enhacement_data$timing <-
tcta_addition_enhacement_data$`Phase (s)`
additional_enhacement_data <- rbind(tcta_addition_enhacement_data,
all_enhancement_data)
additional_enhacement_data$`Participant ID` <-
as.factor(additional_enhacement_data$`Participant ID`)
additional_enhacement_data <- as.numeric(additional_enhacement_data)
```

```
#test <- data.frame(levels(all_enhancement_data$`Participant
ID`),0,"EVAR Lumen",0)
#colnames(test) <- c("Participant ID","Phase (s)","Enhancement
(HU)","timing")
#?rbind()
#a<-merge(test, all_enhancement_data)
#Analysis
#Primary Outcome
print("Graft Related Endoleaks - CEUS Index, tCTA as Refference")
acc.1test(GREL_tab)
#miss one out Cross validation - This is a binary test ?what is
correct method of cross validation
x<- nrow(ceusvtcta)
y <- c(2:x)
a <- ceusvtcta [c(2:x),]
a <- tab.1test(d=na.omit(a$`tCTA Graft-Related Endoelak
(True/False)`),y=na.omit(a$`CEUS Graft-Related Endoleak
(True/False)`))
a <- acc.1test(a)
sensitivity <- a$sensitivity
specificity <- a$specificity
ppv <- a$ppv
npv <- a$npv

for(j in y){
  #a<-ceusvtcta[(j:x),]
    a <- ceusvtcta [c(0:(j-1),(j+1):x),]
    a <- tab.1test(d=na.omit(a$`tCTA Graft-Related Endoelak
(True/False)`),y=na.omit(a$`CEUS Graft-Related Endoleak
(True/False)`))
    a <- acc.1test(a)
    sensitivity <- rbind(sensitivity, a$sensitivity)
    specificity <- rbind(specificity, a$specificity)
    ppv <- rbind(ppv,a$ppv)
    npv <- rbind(npv,a$npv)
    rm(a)
      }
sensitivity <- na.omit(sensitivity)
specificity <- na.omit(specificity)
ppv <- na.omit(ppv)
npv <- na.omit(npv)
# ????i assume its the mean value used for the cross validation
summary(sensitivity)
summary(specificity)
summary(ppv)
summary(npv)

#Diagnostic values
#tCTA as Refference
print("Any Endoleaks - CEUS Index, tCTA as Refference")
acc.1test(ANYEL_tab)
print("Type II Endoleaks - CEUS Index, tCTA as Refference")
acc.1test(T2EL_tab)
#Final DIagnosis as Refference
print("Graft Related Enoleaks - tCTA Index 1, CEUS Index 2, Final
Diagnosis as Refference")
acc.paired(GRELFD_tab)
print("Any Enoleaks - tCTA Index 1, CEUS Index 2, Final Diagnosis as
Refference")
acc.paired(ANYELFD_tab)
print("Type II Enoleaks - tCTA Index 1, CEUS Index 2, Final Diagnosis
as Refference")
```

```
acc.paired(T2ELFD_tab)

#exploratory analysis for association
#data processing for correlation between CEUS and tCTA
correlation <- merge(ceus, tcta_monitoring, by="Participant ID")
correlation$`CEUS Run One (Recording)- Contrast Arrival (s)` <-
as.numeric(correlation$`CEUS Run One (Recording)- Contrast Arrival
(s)`)
correlation$`CEUS Run Two (Recording)- Contrast Arrival (s)` <-
as.numeric(correlation$`CEUS Run Two (Recording)- Contrast Arrival
(s)`)
correlation$`CEUS Run One Temporal Delay (s)` <-
as.numeric(correlation$`CEUS Run One Temporal Delay (s)`)
correlation$`CEUS Run Two Temporal Delay (s)` <-
as.numeric(correlation$`CEUS Run One Temporal Delay (s)`)
correlation$`CEUS Run One (Operator) - Temporal Delay (s)` <-
as.numeric(correlation$`CEUS Run One (Operator) - Temporal Delay (s)`)
correlation$`CEUS Run Two (Operator) - Temporal Delay (s)` <-
as.numeric(correlation$`CEUS Run Two (Operator) - Temporal Delay (s)`)

data <-data.frame(correlation$`tCTA Time For Monitoring to Trigger
i.e. >90HU (s)`, correlation$`CEUS Run One (Recording)- Contrast
Arrival (s)`, correlation$`CEUS Run One (Operator) - Temporal Delay
(s)`,correlation$`CEUS Run One Temporal Delay (s)`)
colnames(data) = c("tCTA","CEUS","OP_TD","rec_TD")
data1 <- data.frame(correlation$`tCTA Time For Monitoring to Trigger
i.e. >90HU (s)`, correlation$`CEUS Run Two (Recording)- Contrast
Arrival (s)`, correlation$`CEUS Run Two (Operator) - Temporal Delay
(s)`,correlation$`CEUS Run Two Temporal Delay (s)`)
colnames(data1) = c("tCTA","CEUS","OP_TD","rec_TD")
data2 <- rbind(data,data1)
data2

#Correlation plot between time for contrast to arrive in STENT in CEUS
vs time to trigger tCTA
qq1 <- ggqqplot(data2$tCTA, ylab = "Time after contrast injection
started to trigger tCTA (s)")
qq2 <- ggqqplot(data2$CEUS, ylab = "Time after contrast injection
strated till contrast seen in EVAR lumen on CEUS (s)")
qq <- ggarrange(qq1,qq2,ncol=2)
ggsave("contrast_in_endoleak_qqplots.png", qq, device = NULL, path =
NULL,
       scale = 1, width = 210, units = "mm",
       dpi = 600, limitsize = TRUE)
ggplot(data2, aes(x=data2$tCTA,y=data2$CEUS))+
 geom_point()+
  geom_smooth(method = "lm")+
xlab("Time for density to >90HU in monitoring for tCTA (s)")+
ylab("Time for contrast to arrive in EVAR stent\ngraft after injection
in CEUS (s)")


#correlation plot between time for contrast in endoleak on CEUS and
tCTA
colnames(tcta_ceus_timings) <- c("tCTA","CEUS")

qq1 <- ggqqplot(tcta_ceus_timings$tCTA, ylab = "Time for contrast into
tCTA endoleak (s)")
qq2 <- ggqqplot(tcta_ceus_timings$CEUS, ylab = "Time for contrast into
CEUS endoleak (s)")
qq <- ggarrange(qq1,qq2,ncol=2)
ggsave("contrast_in_endoleak_qqplots.png", qq, device = NULL, path =
NULL,
```

```
scale = 1, width = 210, units = "mm",
dpi = 600, limitsize = TRUE)

ggscatter(tcta_ceus_timings, x="tCTA", y="CEUS", xlab = "Time for
contrast into CEUS endoleak (s)", ylab = "Time for contrast into CEUS
endoleak (s)", add = "reg.line", conf.int = TRUE, cor.coef = FALSE,
cor.coeff.args = list(method = "pearson", label.x.npc = "middle",
label.y.npc = "top"))
ggsave("correlation_of_endoleak_timing.png", plot = last_plot(),
device = NULL, path = NULL,
       scale = 1, width = 210, units = "mm",
       dpi = 600, limitsize = TRUE)

##Perfusion phases
#individual patoemt plots
ggplot(all_enhancement_data, aes(x=all_enhancement_data$`Phase (s)`,
y=all_enhancement_data$`Enhancement (HU)`,
col=all_enhancement_data$Measurement))+
  geom_jitter()+
  theme(legend.position="bottom")+
  xlab("Time Since tCTA Phase Triggered (s)") +
  ylab("Enhancement (HU)")+
  guides(color=guide_legend(title=""))+
  facet_wrap(~ all_enhancement_data$`Participant ID`)+
  geom_line()

ggsave("perfusion_by_participant.png", plot = last_plot(), device =
NULL, path = NULL,
       scale = 1, width = 210, height = 297, units = "mm",
       dpi = 600, limitsize = TRUE)
# by type from 9oHU trigger
ggplot(all_enhancement_data, aes(x=all_enhancement_data$`Phase (s)`,
y=all_enhancement_data$`Enhancement (HU)`,
col=all_enhancement_data$`Measurement Class`), xlim=25)+
  geom_point(show.legend = FALSE)+
  geom_smooth(method = loess, formula=y~log(x+1), span=1, se=TRUE)+
  ##bestfit line chosen entirley vissually
  theme(legend.position="none")+
  xlab("Time Since tCTA Phase Triggered (s)") +
  ylab("Enhancement (HU)")+
  xlim(0,80)+
  facet_wrap(~ all_enhancement_data$`Measurement Class`)
ggsave("perfusion_by_type.png", plot = last_plot(), device = NULL,
path = NULL,
       scale = 1, width = 210, units = "mm",
       dpi = 600, limitsize = TRUE)

# by time from start of injection
ggplot(additional_enhacement_data,
aes(x=additional_enhacement_data$timing,
y=additional_enhacement_data$`Enhancement (HU)`,
col=additional_enhacement_data$`Measurement`), xlim=25)+
  geom_point(show.legend = FALSE)+
  #geom_smooth(method = loess, formula=y~log(x+1,10), span=1,
se=FALSE)+
  theme(legend.position="none")+
  xlab("Time Since tCTA Contast Injection Started (s)") +
  ylab("Enhancement (HU)")+
  xlim(0,110)+
  facet_wrap(~ additional_enhacement_data$`Measurement`)
ggsave("perfusion_by_type_from_injection.png", plot = last_plot(),
device = NULL, path = NULL,
       scale = 1, width = 210, units = "mm",
```

```
       dpi = 600, limitsize = TRUE)
## by LOg10 of time from start of injection
additional_enhacement_data$sr <-
log10(additional_enhacement_data$timing)
ggplot(additional_enhacement_data,
aes(x=additional_enhacement_data$sr,
y=additional_enhacement_data$`Enhancement (HU)`,
col=additional_enhacement_data$`Measurement`), xlim=25)+
  geom_point(show.legend = FALSE)+
  geom_smooth(method = 'lm', formula=y~poly(x-1,2), se=TRUE)+
  theme(legend.position="bottom")+
  xlab(expression(paste("Log 10 "^"(Time Since tCTA Contast Injection
Started (s))")))+
  ylab("Enhancement (HU)")+
  guides(color=guide_legend(title=""))+
  facet_wrap(~ additional_enhacement_data$`Measurement`)

ggsave("perfusion_by_type_from_injection_transformed.png", plot =
last_plot(), device = NULL, path = NULL,
       scale = 1, width = 210, units = "mm",
       dpi = 600, limitsize = TRUE)

# by time from start of by Class
ggplot(additional_enhacement_data,
aes(x=additional_enhacement_data$sr,
y=additional_enhacement_data$`Enhancement (HU)`,
col=additional_enhacement_data$`Measurement`), xlim=25)+
  geom_point(show.legend = FALSE)+
  geom_smooth(method = 'lm', formula=y~poly(x-1,2), se=FALSE)+
  theme(legend.position="bottom")+
  xlab(expression(paste("Log 10 "^"(Time Since tCTA Contast Injection
Started (s))")))+
  ylab("Enhancement (HU)")+
  guides(color=guide_legend(title=""))+
  facet_wrap(~ additional_enhacement_data$`Measurement Class`)

ggsave("perfusion_by_class_from_injection_transformed.png", plot =
last_plot(), device = NULL, path = NULL,
       scale = 1, width = 210, units = "mm",
       dpi = 600, limitsize = TRUE)
```

7. Full Data From Prospective Comparative Study

A copy of the following file is on the accompanying CD in the pocket attached to the inside back cover.

CD\ceus_tcta\final_data.xlsx