The Use of Intravascular Ultrasound Imaging in Peripheral Arterial Endovascular Interventions

by

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ABSTRACT

Endovascular intervention is the most common method of treating peripheral arterial disease but restenosis rates remain high. There is limited retrospective evidence suggesting that the use of intravascular ultrasound (IVUS) may improve outcomes of lower limb interventions. Calcium and dissection are important factors in endovascular intervention, but there is a lack of objective data to assess the available classification systems. Estimation of atheroma volume may have value in PAD (peripheral arterial disease), but it is unclear if IVUS is suitable for this purpose.

The aims of this research were: to investigate whether the use of IVUS in femoropopliteal artery interventions can lower the rate of binary restenosis; to investigate how well calcium scoring systems categorise calcium severity; to compare the performance of the two available dissection classifications at categorising dissection; and to investigate whether IVUS is technically adequate for atheroma volume estimation.

Patients undergoing endovascular interventions for occlusive femoropopliteal disease, at a single site, were recruited into a randomised clinical trial (RCT). Participants were randomised into a control group (treatment guided by angiography) and a treatment group (guidance by both angiography and IVUS). Target sample was 150 participants and interim results for 107 participants are presented. Participants were followed with regular duplex ultrasound surveillance to 12 months by providers blinded to the randomisation. The primary outcome was binary restenosis (duplex ultrasound PVR ≥ 2.4) within 12 months with survival analysis using Kaplan-Meier graphs and difference in survival tested with Log-rank test (interim analysis significance p=0.01).

IVUS from 60 consecutive cases from the RCT were analysed for evidence of calcium and dissection. Angiograms were assessed by two independent blinded raters and scored using multiple calcium and dissection classification systems. Angiographic grading of severity was assessed using the IVUS data and grading scores were tested for inter-rater reliability. IVUS from 38 consecutive cases were analysed for adequacy for use in volume analysis.

In the RCT, freedom from binary restenosis was 77.8% in the treatment group and 56.6% in the control group (p=0.007). Randomisation to the treatment group and the use of drug-coated balloons (DCB) were the only procedural parameters to be predictors of reduced rate of restenosis. There was a lower rate of restenosis for participants in the treatment group treated with DCB.

The hybrid CTA/angiography Fanelli system was the only scoring system that was able to differentiate IVUS calcium measurements between mild and severe grades of calcification. Inter-rater reliability was fair/moderate for all scoring systems. Dissection classification systems had good agreement for grading severity but no differences in the IVUS measurements were found

between severe and mild grades for either system. Most IVUS scans were not adequate for estimating atheroma volume.

In conclusion, the lower rate of restenosis in the participants with IVUS guidance suggests that the use of IVUS may be beneficial in femoropopliteal disease. Analysis using IVUS suggests that scoring systems incorporating CTA may be better at differentiating calcium severity. Dissection grading systems agree well but may not differentiate severity of dissections. Peripheral IVUS image quality is probably inadequate for estimating atheroma volume.

DECLARATION

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

5 August 2019

Date

TERMS AND DEFINITIONS / GLOSSARY

ACEi	Angiotensin converting enzyme inhibitors
ACC	American College of Cardiology
AICL	Atherosclerosis Imaging Core Laboratory
BMS	Bare metal stent
CAD	Coronary artery disease
CI	Confidence interval
CLI	Critical Limb Ischaemia
CONSORT	Consolidated Standards of Reporting Trials
CoV	Coefficient of variance
CSA	Cross-sectional area
CTA	Computed tomography angiography
CTO	Chronic total occlusion
DCB	Drug-coated balloon
DES	Drug-eluding stent
DM	Diabetes Mellitus
EEL	External elastic lamina
EEM	External elastic membrane
HT	Hypertension
ICC	Intra-class correlation coefficient
IEL	Internal elastic lamina
IHD	Ischaemic heart disease
IQR	Inter-quartile range

ISR	In-stent restenosis
IVUS	Intravascular ultrasound
LLL	Late lumen loss
MAE	Major adverse event
MLA	Minimum lumen area
MRI	Magnetic resonance imaging
MSA	Minimum stent area
mTOR	Mammalian target of rapamycin
NHLBI	National Heart Lung and Blood Institute
NIH	Neointimal hyperplasia
OCT	Optical coherence tomography
OR	Odds ratio
PACSS	Peripheral arterial calcium scoring system
PAD	Peripheral arterial disease
PARC	Peripheral Academic Research Consortium
PCI	Percutaneous coronary intervention
POBA	Plain old balloon angioplasty
PTmax	Plaque thickness maximum
PTmin	Plaque thickness minimum
PVR	Peak velocity ratio
QCA	Quantitative coronary analysis
QVA	Quantitative vessel analysis
RCT	Randomised controlled trial

ROC	Receiver operating characteristic
SEE	Standard error of the estimate
SFA	Superficial femoral artery
SAHMRI	South Australian Health and Medical Research Institute
TASC	Trans-Atlantic Inter-Society Consensus
TLR	Target Lesion Revascularisation
VH	Virtual Histology

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1 INTRODUCTION

Peripheral artery disease (PAD) represents a significant and growing health burden with a global prevalence estimated at 200 million in 2010, an estimated increase of 23.5% since 2000(1). Endovascular intervention has become the preferred treatment for patients with occlusive disease in the infra-inguinal arteries with rapid growth over the last 20 years(1). A wide range of endovascular treatment devices have become available for use in the peripheral arteries over the last 15 years however high rates of restenosis(2-4) are still present and the lack of durability of these treatments remains a significant problem.

IVUS has been used in the coronary arteries for many years. There is evidence from the coronary intervention literature that the use of IVUS modifies treatment in up to 74% of cases(5) and can reduce rates of restenosis, revascularisation and major adverse events(6). In comparison to angiography, IVUS has been shown to be more accurate at measuring vessel and lesion dimensions, characterising disease and assessing the results of treatments(7-13). For these reasons IVUS has been proposed as a potential method for improving treatment outcomes in the peripheral arteries(14, 15). Retrospective studies have suggested that the use of IVUS can improve outcomes of peripheral endovascular interventions(16), but there is currently no prospective evidence available to support the use of routine use of IVUS in peripheral endovascular interventions. The superior image quality of IVUS can also potentially assist in improving the understanding of other aspects of endovascular treatment.

In this thesis, the primary question that the research sought to answer was whether femoropopliteal artery interventions using combined IVUS and angiographic imaging result in a lower rate of binary restenosis within 12 months for patients with severe claudication or CLI compared to interventions utilising angiography only.

The use of IVUS in the femoropopliteal arteries also provided an opportunity to investigate some other questions related to vessel wall calcium, post-treatment dissection and atheroma volume estimation. Vascular calcification is extremely common in patients with PAD and is known to reduce the success of endovascular interventions(17). There are a number of systems for scoring calcium severity but little is known about their comparative performance. A study was therefore undertaken to investigate the following research question: are IVUS calcium parameters different between grades of severity of calcium scoring systems and how reliable are these systems at classifying severity in the femoropopliteal arteries?

Dissection after endovascular treatment is a common cause of treatment failure(18-20) . There are two classification systems currently available but there is no data on how well they agree at

classifying severe dissections. This makes assessing dissection results between studies difficult. Understanding how well these systems agree at classifying dissection severity would assist interpretation of study results. A study was therefore undertaken to answer the following research question: are there significant differences in IVUS anatomical parameters for severe dissection between the two classification systems and are there differences in inter-rater reliability between the systems?

The use of atheroma volume estimation using IVUS measurements has been reported for the comparison of atheroma burden between different circulations and to assess the effectiveness of atherectomy(21-23) . The little data available suggests that IVUS imaging in the peripheral arteries may not be of suitable quality for volume estimation (24). The final study in this thesis sought to answer the following research question: How many cases undergoing IVUS during peripheral endovascular intervention have an adequate proportion of suitable images for performing atheroma volume analysis?

This thesis is structured as follows: first, a literature review of the current evidence of IVUS in the peripheral arteries will be presented, including the use of IVUS in peripheral arteries, current evidence of how the use of IVUS may affect outcomes, vascular calcification, post-treatment dissection and IVUS-based atheroma volume analysis. Second, there are two chapters reporting the methods and results of a randomised clinical trial (RCT) investigating whether the use of IVUS can reduce the rate of binary restenosis in the femoropopliteal arteries. Third, three chapters reporting studies utilising IVUS imaging to investigate the performance of scoring systems at grading calcium severity, a comparison of dissection classification systems and the suitability of IVUS imaging for the estimation of atheroma volume. A conclusion, summarising the findings from these studies and their implications is also presented.

2 LITERATURE REVIEW

2.1 Introduction

The aim of this literature review is to summarise the current state of knowledge regarding the use of intravascular ultrasound (IVUS) in the endovascular treatment of peripheral arterial disease (PAD) in relation to the research questions set out in Chapter 1. The primary research question of this thesis therefore asks whether the addition of IVUS imaging to femoropopliteal endovascular interventions results in reduced rates of restenosis. The primary focus of this review will therefore be on the use of IVUS in the treatment of stenotic and occlusive disease in the femoropopliteal arteries.

Additional research questions addressed in this thesis investigate using IVUS to assess the grading of vascular calcification, classification of post-treatment dissection, and the suitability of core laboratory analysis methods for obtaining volumetric data from peripheral artery IVUS imaging. The evidence related to these questions will be reviewed within the scope of this literature review.

Reviews of the epidemiology of PAD, the development and current status of endovascular interventional procedures, and the development and current status of IVUS technology are included in the appendices to this thesis (see Appendix 1 and Appendix 2).

2.2 IVUS imaging in treatment of peripheral arterial disease

The following sections will review the current evidence related to the primary research question of this thesis, i.e. whether the use of IVUS reduces the rate of restenosis in endovascular treatment in the femoropopliteal arteries. To allow a full assessment of the evidence related to this question, the following topics will be reviewed: the performance of IVUS at characterising vessel anatomy and pathology, IVUS imaging of specific treatment technologies, and evidence related to the effect of the use of IVUS on outcomes. This review will primarily focus on evidence from the femoropopliteal arteries however evidence from other vessels such as the coronary, iliac and tibial arteries will be discussed when relevant.

2.2.1 Clarification of IVUS terminology

Prior to discussing the evidence for the use of IVUS endovascular interventions it is necessary to clarify some of the specific terminology has been developed to help define and describe various aspects of IVUS imaging. There is substantial variability in terminology used when reporting IVUS, particularly in the earlier years of development of the technology. This was a natural consequence of groups of investigators independently exploring this new technology and having to create new

terminology to describe and define new parameters that hadn't been used before. A consensus statement 2001 from the American College of Cardiology (ACC) set out standards for the performance of coronary IVUS and included guidelines for standard terminology(25). To reduce the potential for confusion when discussing the IVUS literature, terminology has been standardised in this review and in general follows the ACC consensus recommendations. When non-standard terms have been used these have been changed to the standardised terminology unless it is unclear whether the author's terminology is the same as the consensus terminology or when a unique parameter is being discussed that is not covered in the consensus document.

When the total vessel size is being quoted, i.e. the vessel including the lumen, any atheroma present and the media, this is variously termed the external elastic lamina (EEL), external elastic membrane (EEM), the media-bounded area/diameter, the vessel area or the total vessel area. In this review EEM will be used unless it is clear that the term being used is describing a different type of measurement.

The lumen is most commonly termed the "lumen" and this is the term that is used in this review. The term "free lumen" is also encountered and sometimes is not clearly defined. It is often used in reference to post angioplasty appearances and in this context refers to the lumen that lies centrally within the vessel(26), i.e. central to the plaque, in contrast to "neolumen" which is a term sometimes used to describe the luminal space between plaque and the vessel wall created by circumferential dissection after angioplasty(27). "Free lumen" and "neolumen" are not terms defined in the ACC consensus guidelines but will be used in this review when required.

The atheroma area measured by IVUS is actually the atheroma and the media, but it is not possible to delineate the boundary between the atheroma and the media reliably with IVUS. The atheroma area is therefore usually considered to be all the material bounded by the intima and adventitia and the terms "plaque plus media" or "atheroma" have been used as recommended by the ACC. In general, the terms "atheroma" and "plaque" can be used interchangeably as recommended by the ACC as this is the case for this review. Atheroma descriptions vary considerably in the literature. The ACC recommendations of "soft" (echolucent), "fibrous", "calcific" and "mixed" have been used where possible. Due to the subjective nature of atheroma characterisation other terms have been retained whenever there was doubt about the characteristic being described. The term "hard plaque" has been changed to "calcific" when it is clear from the author's definition that this is what the term actually describes and retained when the definition is not clearly stated.

Terminology of post-treatment wall and plaque damage is also variable. Some studies differentiate between fractures (radial disruption of plaque) and dissection (circumferential disruption) while

others use terms like “wall damage.” The ACC guidelines do not differentiate between fractures and dissection. In general, the original terminology has been retained in this review due to uncertainty about the authors’ intentions.

Dimensions are usually expressed as a diameter or an area depending on the measurement method used in the study. The units quoted are those originally used in the source documents. Most studies use mm and mm^2 for diameter and area. Length measurements are more evenly divided in studies between mm and cm and both have been used in this review.

2.2.2 Limitations of angiography in characterising arterial anatomy and pathology

Until the widespread availability of IVUS in the early 1990s, angiography was the only available means for imaging arteries during endovascular interventions and development of endovascular techniques had been entirely dependent on angiography as the imaging modality. Despite the central role of angiography in endovascular procedures, the limitations in angiographic imaging had been recognised for some time (28-31).

These limitations stem from two fundamental features of angiography. These are its dependence on contrast opacification that limits imaging to the lumen, with the vessel wall being invisible, and the planar nature of the imaging that can only provide a two-dimensional image(31). Due to these limitations angiograms are sometimes termed “lumenograms” to emphasise the circumscribed nature of the information provided in these images. Comparison of angiographic findings with histopathological analysis of coronary artery autopsy specimens have demonstrated that apparently normal vessel segments on angiography may have significant disease, with the degree of stenosis under-estimated by angiography(32). Angiography is also limited in defining disease severity in tortuous or irregular vessels(33).

Suboptimal opacification with contrast also limits the accuracy of angiographic measurements. This is a common occurrence in the infra-inguinal arteries, particularly in arteries with severe stenosis or occlusion, and can result in under-estimation of vessel size even when quantification software is used (34).

These problems have resulted in marked disagreement in the assessment of vessel disease between angiography and histology. Isner et al.(35), found disagreement in coronary artery stenosis assessment between angiography and histology in 64% of cases and considerable variation in stenosis estimation between observers, with disagreement in classification of stenosis by at least two of three observers in all cases. Zir et al.(36), also reported considerable inter-observer variability with disagreement in almost half of the cases in a study of coronary

angiograms viewed by four observers. Herrman et al.(28), evaluated reliability in 200 coronary artery angiograms between two observers and found poor agreement with a kappa value of 0.33. Galbraith found disagreement in false-positive or false-negative interpretations in 50% of the cases(37).

These studies were obtained from coronary artery specimens and equivalent data for the peripheral arteries was lacking until Kashyap et al. (38), compared angiographic findings of "normal appearing" segments of lower limb arteries with histological analysis of the same arteries obtained after above knee or below knee amputation. Significant discrepancies were found for vessel diameter, stenosis estimation, concentricity of plaque and calcium severity.

An important caveat to all studies using histology of vessel specimens obtained at autopsy is the potential for changes in vessel shape and dimensions during specimen preparation (39). This creates a degree of uncertainty about the actual relationship between the actual in-vivo vessel dimensions and measurements acquired by angiography.

In addition to the problems of attempting to define a three-dimensional structure by means of a two-dimensional imaging technique, there are also variations in measurement methodologies for assessing the angiographic image. In everyday peripheral vascular practice vessel sizing is often based on visual estimation or "eye-balling" against a reference structure such as a radio-opaque rule (40). A major problem with this technique is that the ruler must be at the same level as the vessel to ensure that differences in the degree of geographic magnification are eliminated. A ruler under or on top of the patient will result in under- or over-estimation of vessel size due to the effects of magnification. Visual estimation has been shown to be the least accurate method for measuring vessel size (41). This is not an abstract problem as appropriate matching of balloon or stent to the vessel size is considered a key element in effective endovascular treatment. A study of porcine peripheral arteries found a significant correlation between in-stent restenosis an over-sizing of nitinol stents (42) and the VIPER (Viabahn Endoprosthesis with Heparin Bioactive Surface in the Treatment of Superficial Femoral Artery Obstructive Disease) study found that in 40% of cases with femoropopliteal disease treated with a covered stent the vessel lumen diameter was over-estimated by >20% resulting in over-sizing and significantly poorer patency rates (43).

Quantitative vascular analysis software has been shown to be superior to subjective measurement methods (41, 44, 45), with the two most common methods used for lumen detection, videodensitometric and edge detection, having equivalent performance (46). Comparison between IVUS and angiographic estimation of lumen size found only moderate agreement between either quantification method and IVUS measurements ($r=0.44$ for videodensitometry and $r=0.47$ for edge detection) (46). This suggests that there are inherent limitations of angiographic measurement

regardless of which method of quantitative analysis is used.

2.2.3 Validation of IVUS against histopathology and phantoms

The development of high resolution IVUS technology provided a new in-vivo method to investigate vessel anatomy and pathology in a format that was similar to that used in histopathology studies. IVUS investigations involving phantoms and autopsy specimens have been undertaken to validate the accuracy of IVUS measurements and assess its ability to define wall and plaque characteristics.

Studies comparing IVUS measurements with phantoms confirmed that IVUS measurements were very accurate, with excellent agreement between IVUS and phantoms. Phantom studies using rigid, straight tubes found excellent correlation between IVUS and actual lumen dimensions (r=0.98-0.99), good reproducibility (coefficient of variance (CoV)= 2.5-5.2%) and low inter- and intra-observer variation (r=0.92-0.99) for a range of phantom sizes from 3 to 30mm (47-49).

These early phantom studies utilised rigid, straight tube phantoms under non-flow conditions, with the IVUS catheter placed perpendicular to the axis of the phantom and therefore did not replicate the anatomical or physiological conditions found in-vivo. In the more complex geometry found in actual arteries the IVUS catheter and the vessel wall may not always be aligned and it is likely that some frames will be obtained in “off-axis” planes. Nishimura et al.(47), purposefully placed the IVUS catheter off axis in rigid, straight tube phantoms and demonstrated that lumen area could be over-estimated by 20% with an off-axis angle of 30°. Whilst an off-axis angle as large is this is unlikely to occur in the femoropopliteal artery segment, an angulation of 10° has been shown to be sufficient to cause a measurable increase in lumen area in the coronary arteries(50).

To address the issue of vessel tortuosity and off axis imaging planes in a controlled environment, Cooper et al.(51), created a series of phantoms mimicking the normal shape and bifurcations of the aortoiliofemoral arteries using a pliable plastic with a pump to produce pulsatile flow. This enabled assessment of IVUS measurements in conditions similar to those found in-vivo. There was very good agreement between IVUS and the phantom measurements of vessel size (intra-class correlation coefficient (ICC)=0.89), confirming that IVUS measurements were accurate in complex geometry and variability conditions.

Despite these encouraging findings, consensus guidelines have recommended that reference vessel diameters be obtained in non-tortuous segments with good alignment of the IVUS catheter to the vessel wall(25) and interpretation of IVUS imaging from tortuous vessels should be treated with caution.

IVUS measurements have also been validated against animal models and autopsy specimens.

Hodgson et al.(48), found high correlation between IVUS and animal specimen measurements for lumen area, lumen diameter, vessel diameter and maximum wall thickness (r=0.91-0.98). Moriuchi et al. (52), found good agreement between IVUS and specimen vessel area measurements (mean area=30.9±21.9mm^2 and 30.1±21.1mm^2 respectively) and excellent correlation within (r=0.99) and between observers (r=0.98). Nishimura et al. (47), also found a high correlation between IVUS and histological measurement of lumen area (r=0.98). Gussenhoven et al.(39), examined plaque characteristics of 11 autopsy specimens of coronary and iliac arteries with IVUS and histology and found good correlation between plaque thickness measurements (r=0.847) but more variability between luminal measurements, which was due to considerable variation in vessel shape in the histopathological specimens attributed to shrinkage during fixation.

Nakamura et al. (53), investigated IVUS assessment of plaque volume in specimens that underwent directional atherectomy. The volume of tissue removed from a sample was measured and compared to volume assessment by IVUS and by histology. IVUS correlated well with the actual sample volume (r=0.92) whereas histologic section assessment correlated less well with both the sample (r=0.81) and with IVUS (r=0.74). This confirmed the accuracy of IVUS for assessment of tissue volume and confirmed that IVUS could be used to investigate the mechanisms and performance of atherectomy techniques.

IVUS has also been shown to accurately identify and define arterial wall structures. Gussenhoven et al.(39), was able to clearly identify the layers of the coronary and iliac artery wall and differentiate between various plaque compositions including lipid deposits, fibromuscular lesions and dense fibrous and calcified lesions. Nishimura et al.(47), primarily examining peripheral artery segments, also found that IVUS could demonstrate the three layers of the arterial wall. Comparison with specimens has confirmed that IVUS identification of coronary artery calcification is excellent with sensitivity of 96-100% reported(39, 47, 54, 55).

2.2.4 Reproducibility of IVUS imaging

Multiple studies of coronary IVUS have demonstrated good intra- and inter-observer agreement. Van der Lugt et al.(56), examined coronary specimens that were pressurised to 100mmHg during IVUS imaging and found low inter-and intra- observer-differences in both lumen area and EEM area before and after angioplasty (range of differences=0.0-0.3mm$^{2)}$. Hodgson et al.(48), found high intra- and inter-observer correlation for lumen area, lumen diameter and vessel area. Hausmann et al.(57), also found high intra- and inter-observer correlation(r>0.90) and low differences between measurements (<10%, SD<20%) for quantitative parameters such as lumen and vessel area. Jain et al.(58), found good inter- and intra-observer correlation at both the reference measurement site (r=0.96 and 0.98 respectively) and in the stenotic lesion (r=0.90-0.94 and 0.94-0.97 respectively). Blessing et al.(59), in a study of patients having coronary stenting

found very high intra- and inter-observer correlation for reference vessel area (r=0.92-0.96) and for minimum stent lumen (r=0.97). Peters et al.(60), found consistently low intra- and inter-observer differences for lumen and vessel area (<0.9%). In all of these studies, directly measured parameters such as lumen or vessel area had better agreement than derived parameters such as stenosis, probably due to the compounding effect of differences in the raw measurements for the derived parameters. A common limitation of this data was the use of less than ideal statistical tests for agreement, e.g. the use of Pearson coefficient of correlation rather than more suitable tests such as ICC (61-65). More recently Gaster et al.(66), used more appropriate tests to assess IVUS reproducibility in the coronary arteries and confirmed good inter- and intra-observer agreement.

Agreement and reliability have also been assessed in the peripheral arteries. Gussehoven et al.(26), assessed inter-observer variability and found close agreement for pre-treatment lumen and EEM area measurements (mean difference of 0.6mm^2 and -0.3mm^2 respectively). There was only moderate inter-observer agreement for qualitative parameters such as eccentricity, plaque morphology and dissection (κ=0.54, 0.59 and 0.46 respectively). In a follow-up study by the same group(67), intra- and inter-observers reproducibility was investigated in more detail and it was found that some qualitative parameters had good agreement including identification of soft lesions (κ=0.61), calcific lesions (κ=0.69) and dissection (κ=0.69). Other qualitative parameters had moderate to poor agreement including lesion eccentricity (κ=0.45) and media and plaque rupture (κ=0.25 and 0.04 respectively). There was also a significant difference in assessment of the arc of dissection (CoV=21%), however this assessment was performed using a subjective visual estimation of hours of a clock face rather than quantitative measurement of the arc in degrees and the authors acknowledged that this may have contributed to the moderate reproducibility. Quantitative parameters had good agreement with no significant difference between observers in either the lumen area or the EEM area (mean difference=0.22mm^2 and 0.03mm^2 respectively)(26). In this study two different IVUS machines were used (one rotating transducer and the other rotating mirror configuration) and no difference was found in area estimation between machines confirming that quantitative IVUS measurements is not equipment dependent.

More recently Miki et al.(68), demonstrated excellent intra- and inter-observer reliability for pre-treatment minimum lumen area (MLA) (ICC=0.987 and 0.955 respectively) and for intra- and inter-observer reliability of the minimum stent area (MSA) post stenting (ICC=0.908 and 0.947 respectively). These reliability results were core laboratory adjudicated and are notable because the IVUS imaging was performed using manual pullback. Additionally, these were cases undergoing standard treatment with no special efforts related to image quality that might be expected if the cases were involved in a prospective trial. This suggests that IVUS images produced in “real world” situations can be measured with a high degree of reliability.

2.2.5 Comparison of angiographic and IVUS assessment of vessel measurements and disease severity

Although there are a great many studies that have used IVUS to investigate vessel pathology and treatment methods, the number that specifically compare the performance of angiography and IVUS is much smaller.

Cooper used an anatomical and physiological mimicking phantom (described in section 2.4.4) to compare lumen measurements obtained with uni- and bi-planar angiography and IVUS. IVUS agreed well with actual phantom measurements (ICC=0.87) and was significantly better than that achieved by angiography (ICC=0.82 for bi-planar and ICC=0.73 for uni-planar, p=0.02 and <0.001).

Nissen et al.(69), studied IVUS and angiography in animal arteries and found good correlation in normal arteries but reduced correlation in diseased vessels, with angiography over-estimating the degree of stenosis compared to IVUS.

In the following year, Nissen et al.(13), compared IVUS and angiography in in 8 normal coronary arteries and 43 diseased coronary arteries in-vivo and found good correlation and low variability in vessel diameter in normal vessels (r=0.92 and standard error of the estimate (SEE)=0.21mm) but found reduced correlation in more diseased, eccentric vessels (r=0.77) with greater variability between imaging modalities (SEE=0.49mm). The performance was worse for estimation of stenosis severity worse with reduced correlation (r=0.63) and high variability (SEE=10.9%). They also noted that “angiographically normal” segments often demonstrated plaque on IVUS and that in most patients it was difficult to find any segments free of disease on IVUS. This was the case even in patients who had disease limited a single site on angiography.

St. Goar et al.(7), compared IVUS and angiography in 20 normal coronary arteries and found that while the measurements correlated well (r=0.88), the IVUS measurements were generally larger with a mean difference of 0.5mm. A similar pattern of a reduced correlation for luminal diameters between IVUS and angiography in diseased coronary arteries was found by De Scheerder et al.(70), with only moderate correlation prior to treatment (r=0.467) and weak correlation after angioplasty (r=0.282). Poor correlation between angiography and IVUS appearances after coronary angioplasty and better sensitivity to evidence of wall damage with IVUS has been confirmed by multiple investigators (13, 54, 71-73).

Nakamura at al(8), found poor correlation between modalities for minimum lumen diameter and lumen cross-sectional area (r=0.05 and r=0.28 respectively) when dissection to the media was present and concluded that this was due to contrast within the dissection plane causing an over-estimation of the lumen on angiography.

Briguori et al.(74), in a large study of 1580 coronary artery lesions in 1297 patients who had both IVUS and angiographic imaging, found that the difference between lumen and vessel wall size was greater in “small” arteries and that the difference in vessel size between “large” and “small” vessels was less than that suggested by the lumen. They concluded that small arteries are often large arteries with more extensive diffuse disease and that larger balloon-to-artery ratios, above the standard 1.10 ratio(75, 76), may be more suitable in these vessels. More recently, Takagi et al.(77), compared quantitative angiographic and IVUS measurements of the coronary arteries and found only moderate correlation (r=0.649, p=0.001) and a mean discrepancy in lumen diameter of 14.8%.

Coronary studies comparing IVUS and angiography have shown the sensitivity for angiography for detecting vessel wall calcification to be only 45-48%, (9, 78). Concordance between the two imaging modalities for the classification of coronary artery calcification is also poor, with Tuzcu et al.(78), finding agreement in only 50% of cases. Calcium detection by angiography was related to severity, with angiography more likely to detect calcium when the IVUS defined arc of calcification was greater(9, 78).

Studies comparing IVUS and angiography in the peripheral vessels also found that there is significant disagreement in the assessment of diseased vessels between IVUS and angiography. Davidson et al.(79), examined 86 arterial segments in a range of peripheral vessels. They found good correlation between modalities (r=0.87) but moderate variability (SEE=1.25mm) for vessel <10mm in diameter. Significant differences in identification of plaque were also noted, with IVUS identifying plaque in 46% of cases that were normal on angiography. In a further study the same investigators also found poor correlation for lumen diameter and area after treatment (r=0.28 and 0.08 respectively)(71).

Tabbara et al.(80), also found that angiography and IVUS in peripheral arteries correlated well in normal arteries, but less so in diseased vessels. They also assessed the ellipticity of the lumen (defined as the maximum diameter/minimum diameter at the same level) and found that lumen assessment by angiography was less accurate in more elliptical lumens.

Van Lankeren et al.(10), compared the performance of IVUS and angiography in 135 superficial femoral arteries in the largest comparison study of the peripheral arteries to date. They confirmed that IVUS detected more diseased vessel segments than angiography (97% vs 83%) and although both modalities found a similar number of eccentric lesions there was in poor concordance with only 51% of eccentric lesions identified on angiography confirmed by IVUS. These results agree closely with a large study by Mintz et al.(81), of 1446 coronary arteries that found a similarly poor concordance for lumen eccentricity between IVUS and angiography and agreement in only 45%

cases.

The sensitivity of angiography for detecting calcification has also been shown to be poor in the peripheral arteries. Van Lankeren et al.(10), found that angiography detected calcification in only 30% of cases with confirmed calcification on IVUS. As in the coronary arteries(9, 78), the sensitivity of angiographic was related to the severity of calcification found with IVUS, with cases where calcification was not identified on angiography having a mean arc of calcification of 92º and cases with calcification identified on angiography having a mean arc of 148º ($p<0.001$).

A weakness of much of the data comparing angiography and IVUS is that most studies date from the 1990s. Since then there have been improvements in both image quality and analysis tools for both IVUS and angiography, as well as significant changes in peripheral endovascular treatment technologies. Unfortunately, there have been few studies comparing IVUS and angiography in the peripheral arteries since 2000.

Tato et al.(82), reported the results of 32 femoropopliteal arteries treated with angioplasty and found a lack of correlation between DSA and IVUS lumen diameter before and after angioplasty ($r^2=0.17$ and $r^2=-0.13$ respectively). Arthurs et al.(11), in a prospective observational study, assessed the relative performance of IVUS and angiography by comparing imaging results in 61 patients having endovascular treatment of the iliac, CFA, SFA and popliteal arteries. There was excellent correlation ($r^2=0.95$) and no significant difference in lumen diameter ($p=0.45$) between angiography and IVUS. IVUS estimation of stenosis estimation was 10% greater than by angiography ($p<0.05$) and the length of stenosis was also longer on IVUS ($p<0.05$). IVUS was only performed prior to treatment so no observations of post-treatment performance could be made. There was a wide range in levels of agreement for qualitative imaging parameters (from $\kappa=0.26$-0.92) emphasising the highly variable nature of angiographic image assessment. There are some limitations to this study that should be considered including the exclusion of larger arteries due to the restricted field of view required by the use of virtual histology (VH) analysis, the exclusion of longer lesions due to the use of mechanical pullback of the IVUS catheter and the use of visual estimation rather than quantitative vessel analysis (QVA) for angiographic measurements.

Hitchner et al.(12), in another prospective observational study, examined angiographic and IVUS imaging of the SFA in 59 patients after endovascular treatment (33 treated with angioplasty and 26 with angioplasty and stenting). All patients had satisfactory appearances on completion angiography. There was a significant difference in lumen area ($p=0.01$) and percentage stenosis ($p=0.03$) between IVUS and angiography. Even though the angiographic residual stenosis was <30% in all cases at completion, all cases had residual stenosis ≥50% on IVUS.

2.2.6 IVUS assessment of arterial remodelling

Arterial remodelling refers to an increase or decrease in the vessel size (i.e. the EEM circumference or area) either in de-novo lesions or as a response to endovascular treatment(83). The accepted terminology for this phenomena is “positive remodelling” when there is an increase in the EEM and “negative” or “constrictive remodelling” when there is a decrease in the EEM(25). Positive remodelling was initially referred to as “compensatory remodelling” as the process was, probably incorrectly, interpreted as a compensatory increase in the vessel size as atherosclerotic plaque increases in volume to maintain lumen size. These processes are invisible to angiography due to the purely luminal nature of this imaging.

Glagov et al.(84), first reported positive hypertrophy in response to the formation of plaque in vessel walls and concluded that hypertrophy can continue until the vessel area has increased by 40% at which point vessel hypertrophy has reached its limit and any further increase in plaque deposition results in a reduction in lumen size.

These findings were confirmed by coronary artery studies of autopsy specimens (85, 86) and in-vivo epicardial ultrasound and coronary artery IVUS (87-89). EEM area was found to increase as plaque area increased, with no change in lumen area, until plaque contributed more than 30% of the EEM area. Once plaque area increased beyond 30%, lumen EEM enlargement ceased and increases in plaque area resulted in a decrease in lumen area. Further studies found that negative remodelling occurs in 20-26% of cases of de novo coronary artery stenosis, with lumen loss being a combination of vessel constriction (EEM decrease) and atherosclerotic plaque (90, 91). In a large study of 603 coronary arteries, Mintz et al.(92), defined negative remodelling as a ratio of lesion EEM to proximal reference EEM of ≤ 0.78, and found this in 15% of coronary artery lesions.

Positive and negative remodelling are regarded as chronological responses to arterial atherosclerotic disease(83), with positive remodelling being associated with unstable lesions earlier in disease progression and negative remodelling being a later manifestation and more likely to be present in older, stable lesions (93-95).

In addition to remodelling due to de novo atherosclerotic disease, it has also become apparent from animal studies that considerable remodelling occurs after angioplasty (96, 97). IVUS imaging found a significant decrease in lumen area and in EEM cross-sectional area when compared to the reference vessel (both $p<0.001$) in re-stenotic lesions in the coronary arteries (98). At the same time there was no significant change in the media plus plaque area. The EEM area was responsible for 83% of the lumen loss with neointimal hyperplasia (NIH) accounting for only 17% of lumen loss, confirming that most of the lumen decrease was due to a decrease in EEM. The mechanisms controlling negative remodelling after angioplasty are poorly understood, although it is

likely that adventitia injury has a primary role, causing activation of adventitial myofibroblasts, modification of the extra-cellular matrix and secretion of pro-inflammatory factors (99).

Positive remodelling was first described in the peripheral arteries by Losordo in 1994(100). Pasterkamp et al.(101), used histopathology of 34 SFA autopsy specimens and IVUS of the SFA in 19 living patients to measure internal elastic lamina (IEL) and lumen area systematically at 5mm intervals along 10-15cm arterial segments. These measurements were compared to a reference site defined as the cross-section with the least amount of plaque. Both enlargement and shrinkage were found in the same arteries. An inverse relationship between the relative IEL area and percentage lumen area stenosis was found with hypertrophy being generally present when the lumen area stenosis was <25% and shrinkage apparent if the lumen area stenosis exceeded 25%. The potential problems with defining the reference site in vessels with plaque present throughout the artery were highlighted by the authors. The same team, in a subsequent study assessing the response to angioplasty, found that while there was an overall positive correlation between plaque area and vessel wall area, no correlation was seen in 60% of cases, suggesting that there is considerable individual variation in the remodelling response(102). Van Lankeren et al.(10), also found that a decrease in EEM area contributed more to lumen stenosis than an increase in plaque area. Van Lankeren et al.(103), performed IVUS on 20 patients at angioplasty and at follow-up (mean of 16 months) and confirmed the role of negative remodelling in restenosis, with plaque area at follow-up unchanged while a decrease EEM was the main contributor to a decrease in lumen area.

2.2.6.1 Implications for vessel sizing

Remodelling represents a challenge for conventional angiography-based vessel sizing. The variable degrees of remodelling can result in highly variable vessel dimensions(101), however the vessel lumen may be a poor indicator of this. There may, therefore, be marked discrepancies between vessel size (i.e. the EMM) on IVUS and the angiographic assessment of the lumen. As highlighted by Schoenhagen et al., angiography may not be able to identify which segments are normal and in many cases there may not be any “normal” reference segments(104).

Sizing of balloons and stents has traditionally been guided by the angiographic reference vessel lumen size but several studies of coronary interventions have confirmed that more aggressive sizing protocols based on IVUS measurements may not only be safe but also lead to improved outcomes(105-108). This has been attributed, in part, to the ability of IVUS to match the balloon size closer to the actual vessel dimensions(106).

2.2.7 The use of IVUS to assess balloon angioplasty

Prior to the development of IVUS imaging, the study of the mechanisms of angioplasty had been

limited to animal studies, angiographic studies and histopathology studies of autopsy specimens. Animal studies have suggested that lumen gain achieved during angioplasty is due to a combination of vessel stretching and fracture of the plaque, intima and media (27, 109-111). These studies have been critical in understanding these processes but are limited by a number of major differences between animal models and atherosclerotic human arteries. These difference include: the mechanisms used for stenosis creation in animal studies, which result in these lesions being stenotic and neo-intimal in nature rather than atherosclerotic; the different biological responses to injury between humans and the various animals used; and the discrepancies in the types and size of vessels used between humans and animal models(112). Autopsy studies have also provided important insights into the mechanisms of angioplasty (113-115) but here also there are some major limitations. Histopathological evaluation of angioplasty is limited by the lack of baseline data and the low proportion of patients who die soon enough after angioplasty to demonstrate acute changes in the vessel(27). This restricts analysis to <0.001% of patients undergoing angioplasty(113), creating a high risk of selection bias. Potential selection bias is exacerbated by the small numbers typically reported in these studies and because all samples are from patients who died and therefore not representative of all patients who had angioplasty(116). The time period between angioplasty and autopsy is also critical. Pathology studies within few days of coronary artery angioplasty have shown significant dissection and plaque disruption (117-120) while very little evidence of vessel disruption is found months after treatment (114). In addition, the specimens are post-mortem and the processes of preparation of specimens has the potential to cause significant artefacts, particularly for quantitative assessment of vessel and lumen size(39, 49).

The development of clinical IVUS imaging provided investigators with the ability to clarify the mechanisms of angioplasty. Almost all coronary artery IVUS studies have confirmed that lumen gain after angioplasty is primarily due to an increase in vessel size (i.e. stretching of the wall), accounting for approximately 70-80% of lumen gain (56, 116, 121-124), with the balance of the lumen gain from a reduction in plaque area (plaque compression).

2.2.7.1 IVUS predictors of restenosis after angioplasty

Jain et al.(58), studied 30 cases of coronary angioplasty with IVUS and found the absence of plaque fractures (radial discontinuity in the plaque), the presence of major dissection (echo-free space behind the plaque extending for more than 90° of the circumference) and higher plaque area to be predictors of restenosis. Tenaglia et al.(125), analysed IVUS imaging of 69 cases of coronary angioplasty and found that the presence of major dissection (defined as extending for >33% (equivalent to >120° of the circumference) to be the only significant predictor of restenosis. Mintz et al.(126), examined 360 coronary artery lesions with IVUS and identified the MLA and residual percentage cross-sectional narrowing (plaque area x 100/ EEM area) as the most powerful

predictors of restenosis. Although 274 of these patients had angioplasty; only 45 had angioplasty without an atherectomy and therefore these results may not be generalizable to stand-alone angioplasty. Peters et al.(127), studied 200 patients who had coronary angioplasty without adjunctive therapies, and found that a larger vessel and lumen area and smaller plaque area were all predictors of larger angiographic diameter at follow-up.

Gussenhoven et al.(26), investigated 39 patients having plain angioplasty treatment of long femoral stenosis (mean length=13cm) with IVUS. IVUS was performed before and after plain angioplasty and the patients were followed for 6 months. Pre-treatment quantitative and qualitative IVUS parameters were not found to be predictors of restenosis. Post-treatment, the free lumen area (the lumen area excluding the area between the vessel wall and dissected plaque), free lumen diameter, and severity of dissection (the arc of dissection in degrees) were found to be the strongest predictors of restenosis. Mean lumen area at the narrowest segment after treatment was 13.2±3.6 mm^2 for cases free of restenosis and 9.7±3.2 mm^2 for cases with restenosis ($p<0.05$). There was no difference in EEM area, plaque area or percentage area stenosis between cases with or without restenosis. The authors concluded that percentage stenosis may be a less accurate representation of actual lumen area because of variations in vessel size due to remodelling.

Van Lankeren et al.(128), assessed IVUS predictors of restenosis after plain balloon angioplasty in the 21 patients with iliac artery disease. Free lumen and EEM areas were larger in cases free of restenosis at six months but this was not statistically significant. This study suggests that the same predictive parameters may apply in the iliac arteries but the sample size was too small to draw any firm conclusions.

Vogt et al.(129), assessed IVUS appearances in 18 patients undergoing femoral angioplasty and found a strong correlation with the severity of calcium and severity of dissection. Unlike Gussenhoven et al.(26), they found dissection of be a negative predictor of restenosis, however this study was limited by small numbers and few cases that developed restenosis.

Van der Lugt et al.(130), reported the largest study evaluating predictors of restenosis after femoral angioplasty in 1998. In total 114 patients were treated with plain angioplasty and assessed at one and six months. The IVUS imaging of these vessels was assessed using a systematic and extensive analysis method involving analysis of images at set intervals throughout the treatment zone of the vessel rather than just at the target lesion as was common in earlier IVUS studies. No angiographic parameters were predictive of restenosis. IVUS based lumen area stenosis after angioplasty was the only independent predictor of anatomic restenosis at both one and six months (odds ratio (OR) 1.16, 95% CI:1.07-1.26, p=0.0001). Mean arc of calcification prior to treatment was an independent predictor of clinical restenosis at one month (OR=1.69 per 30° increase in arc)

but there were no independent predictors of clinical restenosis at six months. The finding that calcification is a predictor for early restenosis is in agreement with angiographic coronary evidence (131). The presence of dissection was associated with lower rates of early restenosis but higher rates of late restenosis.

Inadequate lumen increase is the most consistent reported predictor of restenosis in both the coronary and peripheral arteries. There is no agreed threshold IVUS values for MLA to indicate satisfactory post-angioplasty results. This is true for both plain angioplasty and drug-coated balloon (DCB) angioplasty. None of the studies undertaken have reported receiver operating characteristic (ROC) analysis for establishing cut-off values. Only one study reported mean lumen area values for cases with and without restenosis and this suggested that an area value between 10 mm^2 and 13mm^2 may potentially be a threshold for risk of restenosis after plain angioplasty(26). In the setting of increased use of DCB technology, specific IVUS data for acceptable post-DCB angioplasty appearances is needed and the only criteria currently available for assessment of satisfactory treatment after angioplasty remain the conventional angiographic criteria of <30% residual stenosis and lack of a flow limiting dissection.

2.2.8 The use of IVUS to assess stenting

Angiography assessment of stent deployment in the coronary arteries has been shown to over-estimate the stent lumen diameter, the adequacy of stent expansion and completeness of stent strut apposition (132, 133). This has direct implications for optimal stent deployment, with up to 80% of balloon expandable stents in the coronary arteries requiring further expansion after IVUS despite optimal appearances on completion angiography(132) and IVUS guided stenting resulting in larger minimum lumen diameters (105, 107). Angiography has also been shown to under-estimate in-stent neo-intimal hyperplasia at follow-up(134). The importance of achieving an adequate stent lumen has been demonstrated using IVUS, with stent lumen area being an independent predictor of stent thrombosis(135) and in-stent restenosis(136). There is general agreement that the MLA is a key IVUS criteria for assessing adequacy of stent deployment, however there is no consensus on the values of specific IVUS criteria for adequate stent expansion(137, 138). It is unclear how important stent symmetry is for the IVUS assessment of stent deployment with disagreement of its predictive value(139-141) and there has been a lack of uptake in IVUS-based stent trials(137).

In the peripheral arteries, studies of IVUS in iliac artery stenting have confirmed that IVUS detects more cases of sub-optimal stent deployment. Navaro et al.(142), examined 109 balloon-expandable stents with IVUS immediately after deployment in the iliac arteries. All appeared satisfactory on completion angiography but 27% were sub-optimal on IVUS with most being under-expanded or under-sized and required further treatment. Buckley et al.(143), reported that 40% of

balloon-expandable stents in the iliac artery that appeared to be satisfactorily deployed on angiography were under-expanded on IVUS and required repeat dilation. Schwarzenberg et al.(144), investigated in-stent restenosis in 37 iliac and 24 superficial femoral arteries, treated with self-expanding or covered stents, with IVUS and angiography at approximately15 months after implantation. Angiography and IVUS estimation of percentage restenosis correlated well (r^2=0.96) but angiography systematically under-estimated in-stent restenosis (ISR) by 13% with under-estimations of up to 25% found. Angiography also missed 14 of the 21 cases of inadequate stent expansion. The same authors also assessed covered stent deployment in six iliac arteries and 17 femoral arteries with angiography and IVUS and found that the severity of neo-intimal hyperplasia was greater with IVUS (145).

Long term patency data is available for IVUS guided iliac artery stenting. Kumakura et al.(146), prospectively collected a registry of 455 patients with 507 lesions treated with iliac artery stenting over a 20 years period. In all cases IVUS imaging was used to assist in stent deployment. A variety of balloon-expandable and self-expanding stents were used over this time. Five, 10 and 15 year primary patency were 87%, 83% and 75%. MLA, in-stent thrombosis and calcific lesions were independent predictors of restenosis whereas stent fracture and edge dissection were not predictive. In this study, longer term (>5 years) follow-up data was limited by very few cases at 10 (60 patients) and 15 years (15 patients). Miki et al.(147), reported IVUS findings from a smaller group of iliac stent cases (154 lesions in 122 patients), all of whom had nitinol self-expanding stents deployed, over a shorter period (mean follow-up 39 months) and found that a small MSA (optimal threshold of 17.8mm^2 on ROC analysis) and stent edge dissection were independent predictors of target lesion revascularisation (TLR). Calcific lesions were not an independent predictor of restenosis, but calcific lesions did result in significantly smaller MSA.

The evidence related to IVUS predictors of in-stent restenosis in superficial femoral artery is limited and mixed in nature. Miki et al.(148), retrospectively analysed IVUS imaging of 236 cases of patients who had bail-out stenting with self-expanding bare metal stent (BMS) following angioplasty of the SFA. Due to the lesion lengths involved manual pullback of the IVUS catheter was used for these studies. Patients were followed up for a mean period of 34 months and 42 patients (17.8%) had clinically directed TLR. Total stent length, distal reference EEM and the presence of medial stent edge dissection (dissection reaching the IEL located within 5mm of the stent edge) were all independent predictors of TLR. An ROC analysis was not performed to identify the cut-off value for distal reference EEM, however the distal reference EEM was 32.3±10.7mm^2 in the no-TLR group and 25.1±7.6mm^2 in the TLR group ($p<0.006$) and the cut-off value is therefore likely to be around 30mm^2. Angiography identified stent edge dissection in only 25% of cases where this was seen on IVUS. There was a high proportion of complex cases (>50% with chronic total occlusion (CTO) and 60% Trans-Atlantic Inter-Society Consensus (TASC) II C/D lesions) with

long lesions (mean stented length 170mm and 213mm for non-TLR and TLR groups respectively).

The same group retrospectively studied a group of 97 patients undergoing stenting of the SFA (BMS in 46 cases and drug-eluting stent (DES) in 39 cases), with follow-up by angiography at 6 months(68). Manual pullback IVUS was used to image the treated region at completion and the IVUS images were analysed by an independent core laboratory. 35% of patients had CTO, 36% of lesions were calcified and mean stent length was 144mm. 32% of cases had binary restenosis at 6 months and 8% had a clinically driven TLR. Longer stent length was an independent predictor of ISR (OR 1.08, 95%, confidence interval (CI) 1.01 to 1.16, p=0.04) and an increase in MSA was an independent predictor of lower risk of ISR (OR 0.58, 95% CI 0.41 to 0.82, p<0.01). On ROC analysis the optimal minimum stent lumen threshold for prediction of ISR was 15.5mm^2 (sensitivity 76.0% and specificity 71.4%, area under the ROC curve 0.769), with a significant difference in ISR for MSA <15.5mm^2 (57%) and ≥15.5mm^2 (12.5%), (p<0.001). No angiographic criteria were identified as independent predictors of ISR.

Mori et al.(149), retrospectively assessed 40 patients who underwent IVUS-guided DES placement in the femoropopliteal. Lesion length was 134mm and 109mm for patient with ISR and free of ISR respectively. Distal reference lumen area and axial symmetry index (minimum/maximum stent area) were both independent predictors of ISR. ROC analysis identified a distal reference lumen area of 17.1mm^2 (area under the curve 0.783, sensitivity of 78.6% and a specificity of 72.2%) and an axial symmetry index of 0.6 (area under the curve 0.769, sensitivity of 85.7% and a specificity of 69.5%) to the best cut off values.

The Zephyr trial studied 690 patients undergoing femoropopliteal DES stenting with IVUS imaging available in 586 lesions prior to treatment and 632 lesions after treatment (150). Lesion characteristics included a mean lesion length of 170mm, CTO in 45% of cases and calcification in 65%. Follow-up was completed to one year and independent IVUS predictors of restenosis included lesion length ≥16mm, a MSA ≤12mm^2 distal and reference EEM area ≤27 mm^2. Although angiographic vessel diameter estimation was also associated with a higher risk of restenosis, it was a less reliable predictor, with ROC analysis finding that IVUS data provided a larger area under the curve (0.70 vs.0.65, p=0.04). Restenosis rates were 50% when two of these predictors were present, whereas the rate was 15% when no predictors. Further analysis at two years (151) confirmed the predictive value of a distal EEM area of ≤27 mm^2.

The evidence regarding useful IVUS predictors of ISR from these SFA stenting studies is somewhat mixed. Other than lesion length the most commonly identified parameters were distal reference vessel size (independent predictor of ISR in three of the four studies) and stent lumen area (an independent predictor in two studies). The threshold value for distal reference EEM size is

likely to be between 27-30mm^2. There is some uncertainty about this range due to the lack of ROC analysis in one study (148)). Unfortunately, in one of the studies that reported a threshold value for the distal reference vessel, lumen area rather than the EEM area was used and is therefore not directly comparable with the other two studies(149). The threshold values for minimum stent lumen were 12mm^2 (all cases used DES) and 15.5mm^2 (mixed DES and BMS sample). Patient and lesion characteristics were similar between these two studies (both had a high proportion of longer, more complex lesions) and it is unclear whether the type of stent (BMS vs. DES) had an effect on the threshold values reported.

2.2.9 The use of IVUS to assess atherectomy

In the coronary arteries, it has been confirmed that IVUS can accurately estimate the volume of plaque volume removed during atherectomy (53) and that angiography under-estimates residual stenosis after atherectomy compared to IVUS (angiographic estimation of residual plaque 21% vs IVUS estimation of residual plaque 48%)(152). IVUS has been used in the coronary arteries to confirm the mechanism of treatment in a variety of atherectomy technologies including directional atherectomy (53, 152, 153), rotational atherectomy(123, 154, 155) and laser ablation(154, 156, 157).

Vessel remodelling may be an important consideration when planning atherectomy. There is coronary IVUS evidence that negative remodelling, rather than NIH, is the primary cause of restenosis after directional atherectomy (153). Patients under-going directional atherectomy with IVUS-confirmed negative remodelling had smaller lumen on 6-month follow-up angiography than those without remodelling. It is possible that the reduced effectiveness of directional atherectomy found when negative remodelling was present was due to the smaller proportion of plaque contributing to the stenosis (158). There is no peripheral data on either remodelling after atherectomy or effect on outcomes of performing atherectomy when negative remodelling is present.

Most IVUS studies of atherectomy in the peripheral arteries have involved either rotational or directional atherectomy devices. These are also the most commonly used devices in Australia and the only types available at the site of the research reported in this thesis.

There have been several studies of rotational atherectomy using IVUS. A small study of 6 patients undergoing Jetstream rotational atherectomy of the SFA, popliteal and posterior tibial artery (without adjunctive angioplasty) found a significant increase in lumen area (3.9 to 8.0mm2, p=0.02) after atherectomy, with no increase in overall vessel area (31 to 32.1 mm2, p=0.4). (159). The device had a maximum burr size of 3.0mm and the lumen area at completion corresponded to a mean diameter of 3.2mm, suggesting that the device is restricted to creating a lumen

approximately the same size as the device. In another study, quantitative volume measurements were obtained on 18 patients who underwent atherectomy of the SFA, popliteal artery and tibioperoneal trunk with the Jetstream device(21). Atherectomy achieved a plaque burden volume decrease of 12% (lesion volume decreased from 479mm^3 to 423mm^3) and a lumen increase of 43% (148 to 212mm^3) with no significant increase in vessel size. VH assessment of calcification showed no change in the percentage of calcium after treatment, although caution is required with this finding as this analysis has not be validated for peripheral vessels. No information on the degree of severity of calcification was provided in these two reports but a subsequent study of the Jetstream device reported on calcium removal in 26 patients with calcified vessels(160) and found that rotational atherectomy resulted in a reduction in the calcium area within lesions (77% of lumen increase was attributed to calcium reduction) and modification of the plaque appearances (significant reductions in plaque convexity and surface irregularity). The conclusions related to calcium reduction are limited by an unusual definition of severe calcification (>90degree of the wall and longer than 5mm in length) that is markedly different to commonly quoted definitions of severe calcification (i.e. bilateral calcium and a length of >1-5cm or >50% of the lesion length (17, 161, 162)) and the difficulty of assessing calcium volume caused by the acoustic shadowing artefact due absorption and reflection of the ultrasound beam by calcium(25).

Tielbeek et al.(163) compared directional atherectomy (Simpson Atherocath and Atherotrack devices without adjunctive angioplasty) in a non-randomised study of 18 patients who underwent directional atherectomy of the femoropopliteal artery guided by both angiography and IVUS with a historical comparison group of 22 patients guided by angiography only. Lesions were short (stenosis <5cm and occlusions <2cm) in SFA and the above knee popliteal artery. In both groups atherectomy was continued until a satisfactory luminal enlargement was obtained on angiography. IVUS was then performed in the group receiving angiography and IVUS, and repeat atherectomy was performed until satisfactory IVUS appearances. 15 of 18 with IVUS had repeat passage due to inadequate treatment. Repeat passage due to IVUS resulted in a 15% increase in minimum lumen diameter. There was no significant difference in patency between groups at 1 year (IVUS=57% and angiography 64%). The same authors used IVUS to assess lumen area increase, plaque area reduction and total vessel area in 16 femoropopliteal artery lesions in 12 patients treated with the same atherectomy devices(164). All lesions were treated with 2 or 3 passes with IVUS imaging performed after each pass of the device. Mean lumen increased from 3.8 to 9.8mm^2 and plaque area decreased from 18.1 to 12.8mm^2. Total vessel area showed minimal change, increasing from 21.9 to 23 mm^2. Lesion eccentricity and calcification had no effect on the lumen area increase achieved with atherectomy.

Cioppa et al.(165), studied 30 patients who had IVUS guided atherectomy, from a registry of patients who had combined directional atherectomy (Turbo Hawk Plaque Excision System) and

DCB. Atherectomy was performed under angiographic and IVUS guidance until a residual stenosis of <30% was achieved at which time post dilation with a DCB was performed. Completion angiography and IVUS was then performed to confirm <30% residual stenosis. The majority of the lumen increase was achieved by the atherectomy, with the mean minimum lumen diameter increasing from 1.2mm prior to treatment to 4.2mm after atherectomy and to 5.1mm at completion after DCB dilation. Lumen area was not given but assuming a circular lumen, the estimated atherectomy contribution to lumen area increase was 66% compared with 34% achieved by dilation. Bail-out stenting was only required in two cases with flow-limiting dissection after atherectomy and DCB. Primary patency and TLR rates at one year were 10%. These are very good results given the high-risk nature of this sample (mean lesion length of 115mm and all with severe calcification); however the conclusions from this study are limited by the small sample, unclear selection criteria and lack of control data. The degree of vessel (i.e. EEM) enlargement would have been valuable as an indication of vessel stretching, and therefore barotrauma, however this was not reported.

Excimer laser atherectomy is available in Australia but is limited by the large capital cost of the generator. IVUS was used to assess excimer laser atherectomy of the femoropopliteal arteries in a subgroup of 33 patients from the CELLO registry(166). A significant increase in lumen area was seen post atherectomy (5.5+/-3.3mm2, p<0.0001), with a 24% rate of medial dissection and <1% rate of adventitial dissection as assessed by IVUS.

The Diamondback orbital atherectomy is currently not available in Australia. It uses a burr-type head that rotates in an orbital fashion to grind plaque into microscopic material(167) and is designed to preferentially remove harder, more non-compliant tissue(168). An IVUS study of 24 patients with primarily SFA lesions found a non-significant increase in the minimum lesion area (4.0 to 4.7mm^2, p=0.072) and no change in overall calcium area (as assessed with VH-IVUS) (23).

A report comparing histological and IVUS assessment of cases after directional atherectomy found similar rates of adventitial injury each assessment method (51% vs 56% of cases respectively). Injury identified with IVUS was strongly associated with histopathological evidence (OR 21.1, 95% CI 7.6-57.9, p<0.001), suggesting that IVUS may be able to be used to assess vessel injury instead of histology(169). There may be a role for IVUS guidance when directional atherectomy is used, given that the potential for vessel wall damage appears to be greater after directional atherectomy compared to other types of atherectomy (166, 170, 171) and the evidence that adventitial injury is associated with aggressive restenosis(171-173).

2.3 Does the use of IVUS change outcomes?

The evidence presented above suggests that IVUS is more accurate at assessing the nature and

degree of arterial disease than angiography. It is also able to identify aspects of arterial disease, such as remodelling, that cannot be assessed at all with angiography. IVUS is also able to assess the effect of the various forms of endovascular treatment currently available. It seems plausible that the use of IVUS should enable optimisation of treatments and improve outcomes.

2.3.1 Evidence from the coronary arteries

The experience with IVUS is much more extensive in coronary artery interventions than in the peripheral arteries. Whilst the differences between coronary and peripheral artery disease and treatments must be recognised, experience in the use of IVUS in the coronary arteries may be a useful guide to the potential benefits for outcomes that might result from more extensive use during peripheral endovascular intervention.

From as early as 1993 the GUIDE study demonstrated that the use of IVUS could have an impact on treatment during endovascular therapy of the coronary arteries, with a change in treatment occurring in 48% of cases (152). Treatment modifications reported included more dilatations and larger balloons during angioplasty and more passes during directional atherectomy, with removal of more tissue and treatment of more segments. In the CRUISE study, 525 patients underwent BMS placement in the coronary arteries and found that the use of IVUS resulted in larger MSA and lower TLR rates than when angiography alone was used(105). The CLOUT study(106) investigated using IVUS to size angioplasty balloons during coronary interventions on the basis that the angiographic measurement may under-measure the true vessel dimension when positive remodelling was present. This resulted in up-sizing by a mean of 0.5mm in 73% of cases with the resulting quantitative coronary analysis (QCA) based measured balloon-to-artery ratio increasing from 1.00±0.12 to 1.12±0.13. This over-sizing resulted in an increase in minimum IVUS lumen area (3.16 to 4.52mm^2) and a reduction in residual stenosis (28% to 18%) compared to what was achieved with angiographic sizing based on the lumen diameter. This was achieved without an increase in the post-angioplasty dissection rate and a less than 2% rate of major complications.

A meta-analysis of seven RCTs comparing IVUS and angiographic guidance of BMS in the coronary arteries found that IVUS guidance was associated with significantly reduced rates of 6-month restenosis, re-vascularisation and major adverse cardiac events(174). While BMS and plain angioplasty are no longer standard treatment in the coronary circulation, they arguably represent a treatment paradigm that is closer to current standard peripheral intervention treatments. These results suggest that the use of IVUS could be of benefit for peripheral interventions. Important caveats to this conclusion are the differences in size and haemodynamics between the coronary and peripheral arteries, and the use of self-expanding stents in the peripheral arteries in contrast to balloon-expandable stents in the coronary arteries.

Experience from the DES era of percutaneous coronary intervention (PCI) may also have some relevance for peripheral interventions as drug eluding technology is rapidly becoming the standard of treatment in the peripheral arteries, albeit primarily using DCBs rather than stents. The ADAPT-DES study, based on a registry representing the largest experience with IVUS guided DES therapy, found that there was a change in intervention strategy in 74% of cases when IVUS was performed (5). In this study, the use of IVUS resulted in a larger stent or balloon size being used in 38% of cases, higher inflation pressures in 23%, longer stents in 22%, additional post-stent dilatation due to incomplete expansion or mal-apposition in 7%, and placement of additional stent in 8% of cases.

A recent meta-analyses of IVUS guidance of DES implantation in the coronary arteries have shown a significant reduction in major adverse cardiovascular events(6) and stent thrombosis when IVUS is used.

2.3.2 Evidence from the peripheral arteries

Although the extensive research into peripheral artery IVUS reviewed above has provided valuable insights into disease progression and treatment, there is limited evidence on whether the use of IVUS improves outcomes for peripheral arterial interventions. The role of IVUS in peripheral endovascular practice is currently unclear.

A recent systematic review sought to identify all reports of the effectiveness of IVUS in lower limb endovascular interventions(16). This review identified 13 studies in total, however only eight of were directly related to effect of IVUS use on outcomes. The other five studies investigated the use of an IVUS guided re-entry device during sub-intimal crossing of occlusions and will not be discussed further.

The eight studies identified investigated the use of IVUS to assist treatment for a variety of technologies including angioplasty, stenting and atherectomy. Only three studies included a comparison between angiographic guidance and combined IVUS/angiographic guidance. All three of these studies were retrospective and used a variety of methodologies. As these studies represent the only data available directly comparing outcomes between interventions with and without IVUS imaging, they will be analysed in detail to clarify what we know and don’t know about the effect of IVUS imaging on treatment outcomes in the peripheral arteries.

Buckley et al.(143), retrospectively studied 71 consecutive procedures in 52 patients having stenting of iliac artery stenting for aorto-iliac occlusive disease. IVUS and angiography were used in 49 cases and angiography alone in 22. IVUS demonstrated under-deployment of stents in 40% of cases resulting in repeat dilatation to achieve good apposition. Five-year follow-up was available in 96% of patients and primary patency was higher in patients in the IVUS group (100% vs 69%,

p<0.001). There were no re-interventions required in the IVUS group compared to five in the angiography group (22% re-intervention rate), with four of these cases having under-deployed stents confirmed on IVUS imaging at the time of re-intervention. This study is limited by its retrospective nature, by the potential for bias due the lack of randomisation (the allocation method was not stated) and by the small number of patients in the angiography group. This study suggests that IVUS guidance of stent deployment significantly improves outcomes in the iliac arteries. The applicability of these findings to infra-inguinal endovascular intervention is unclear given the differences in vessel size and haemodynamics, differences in the stenting techniques used and differences in long term outcomes between the iliac and femoral arteries.

Iida et al.(14), retrospectively analysed the use of IVUS in 1198 limbs of 965 patients recorded in a multicentre clinical database dedicated to femoropopliteal stenting. 234 cases where IVUS imaging was used were identified and propensity score-matching was performed to create 234 pairs of cases with and without IVUS imaging. These were then compared to assess results between angiography and combined angiography and IVUS guidance. Analysis at 5 years showed higher primary patency when IVUS was used (65% vs. 35%, p<0.001) as well as significantly better assisted primary patency, secondary patency, freedom from re-intervention, freedom from adverse limb events and event-free survival. Higher primary patency with IVUS use was found regardless of the TASC lesion classification, calcification severity and location suggesting that the use of IVUS may improve outcomes for all levels of lesion complexity and difficulty. All cases had pre-dilation with plain balloon and stenting with self-expanding nitinol stents. Propensity score-matching was used because there were significant differences between the IVUS and non-IVUS groups. IVUS was more likely to be used in more complicated lesions but less likely to be used if there was heavy calcification. IVUS was also less likely to be used in non-ambulatory patients, those on dialysis and those with CLI. This suggests that interventionists were less likely to use it on higher risk patients and the authors suggested that the extra time required for IVUS may have been a factor in these cases (although there was no data to support this conclusion). This study is limited by the retrospective nature of the analysis. The information provided by the database on IVUS imaging was also limited with no details available on why IVUS was or was not used, the nature of the IVUS findings or how IVUS effected the treatments undertaken on patients. There were also a significant number of patients with missing data that were excluded from inclusion in the propensity score matching, introducing a potential bias. It is also possible that bias may also have been introduced by the differences in sample characteristics between IVUS and non-IVUS cases that may not have been accounted for by the propensity matching. In addition, we do not know the usage of IVUS amongst all endovascular procedures as this database represents the subset of patients that had stenting. Stenting was used a “bail-out” option in patients with residual stenosis or dissection and it is therefore conceivable that if IVUS was used in some of these cases it may have

influenced the decision to stent and therefore the inclusion of the case in the database.

Panaich et al.(15), retrospectively examined a cohort from the US Healthcare Cost and Utilization Project Nationwide Inpatient sample database for the years 2006 to 2011. 1299 procedures were identified as having used IVUS from a total of 92,714 peripheral endovascular procedures identified. The primary outcomes of in-hospital mortality and amputation and the secondary outcome of post-procedural complications were compared for patients who had IVUS performed and those that did not have IVUS. There was no significant difference in in-hospital mortality between the two groups (1.1% vs 1.3%, p=0.34) and the use of IVUS was not predictive of lower mortality (OR 1.17, 95% CI 0.73 to 1.87, p=0.51). Lower rates of amputation (5.3% vs. 9.8%, p<0.001) and peri-procedural complications (12.0 vs. 14.5%, p<0.001) were found for the IVUS group. Overall IVUS use was associated with a non-significant increase in total costs of care (UD$21,233 vs. US$20,646, p=0.16). Analysis was also performed using a propensity matched cohort of patients who did not have IVUS performed with broadly similar results. The large number of cases in this database appears impressive; however, the actual number of cases that used IVUS was much lower. The fact that only 1.4% of cases had IVUS performed, and the lack of information about why IVUS was or not utilised, are significant weaknesses of this study. While this study suggests that there may be benefits from using IVUS, the limitations of the database also restrict its usefulness for informing and guiding practice. The most important limitation was the lack of long-term follow-up after discharge. This resulted in conclusions on amputation being limited to the pre-discharge time frame and a lack of data on other medium or long-term outcomes measures commonly used to assess endovascular procedures, such as patency, binary restenosis and target lesion revascularisation rates. There was also a paucity of procedural detail due to the limitations in the data contained in this database. In particular, there was no information on lesion characteristics and procedural information was limited to whether angioplasty or stenting was used. There was also no data on why IVUS was used in some cases and not in others. It is possible that IVUS was used more often in difficult cases as it was more likely to be used in cases treated with stents and in emergency cases; however this is an inference and cannot be proven from the data available. There was also no information on how IVUS may have changed treatments and therefore no insights into the mechanisms by which the use of IVUS may have improved results.

A further study to comparing outcomes for angiographic vs. IVUS based treatment has been published since the systematic review discussed above. This study was a retrospective analysis of the effect of IVUS guidance on outcomes of 114 patients who were treated with directional atherectomy for in-stent restenosis (ISR) in the femoropoliteal arteries (175). Guidance was either by angiography alone or angiography and IVUS but the reasons for use of one or other form of imaging guidance was not specified. In the angiography group, 68 patients had atherectomy

performed until ≤30% residual stenosis was achieved with subsequent plain angioplasty. In the angiographic and IVUS group 46 patients had atherectomy performed until ≤30% residual stenosis was achieved. IVUS imaging was then performed and the residual stenosis was assessed. If >30% residual stenosis, atherectomy was repeated until IVUS confirmed the residual stenosis was <30%. There were no cases of entrapment of the device in the stent or removal of stent materials in either group. The IVUS guided group had significantly more atherectomy passes (18 vs 8, p=0.02) and a significantly lower rate of clinical directed TLR at one year (17.9% vs 51%, p=0.03). The lack of IVUS was a significant predictor of clinical directed TLR (OR 3.5, 95% CI 1.188-10.32). This study is limited by its retrospective non-randomised design, lack of detail on allocation of treatment and lack of core-lab adjudication. There were some differences in patient characteristics. The IVUS group were significant older by more than six years (p=0.0005) and had higher HDL while the angiography group had higher triglycerides. None of these factors were predictive of TLR. No quantitative data was provided on lumen gain or neo-intimal material removed during atherectomy or on the number of cases that required additional atherectomy passes. Although this study suffers from the limitations of its retrospective design, the results are impressive and provide further evidence that the use of IVUS may confer clinical benefit. These conclusions are specific to treatment of ISR with directional atherectomy and therefore cannot be generalised to other treatment techniques.

These studies represent the only data that assesses the effect of IVUS imaging on lower limb interventions. All these studies suggest that using IVUS may provide benefits however all are retrospective and, as discussed above, are all limited, for a variety of reasons, in their ability to guide clinical practice. The generalisability of the study by Buckley et al.(143) to infra-inguinal disease is unclear as the types of treatment used in the iliac arteries and the response to treatment in these vessels differs from that found in the femoropoliteal artery. The study by Krishnan et al.(175), was restricted to a specific problem and treatment. While it suggests that IVUS can significantly improve the treatment of ISR, this result cannot be extrapolated to other types of atherectomy, other types of disease or non-atherectomy treatment modalities. Both Iida et al.(14) and Panaich et al.(15) explored the use of IVUS via large retrospective databases and both studies lack the detailed procedural data required to guide practice. The evidence to date suggests that IVUS has the potential to improve outcomes of endovascular interventions however the quality of evidence is insufficient to reach firm conclusions. This lack of high quality evidence supporting the use of IVUS is reflected in the only 1.4% of lower limb interventions using IVUS in the USA(15). Prospective randomised studies are required to provide more definitive guidance of the role of IVUS in the peripheral arteries.

2.4 IVUS and angiographic assessment of vascular calcification

The following sections review the current state of knowledge regarding vascular calcification, IVUS quantification of vascular calcification and the performance of calcium scoring systems in the context of the research question: are IVUS calcium parameters different between grades of severity of calcium scoring systems and how reliable are these systems at classifying severity in the femoropopliteal arteries?

2.4.1 Prevalence and clinical significance of vascular calcification

Vessel calcification is a common finding in PAD with a likely prevalence of 30-50% (17). The prevalence may even be higher than this for patients undergoing endovascular interventions as prevalence of calcification increases rapidly with age and has been shown to be present in 70-90% of iliac arteries in patients >60 year of age(176). It is difficult to provide a precise estimate of calcification prevalence in the infra-inguinal arteries due to a lack of studies specifically targeting these vessels, but there is no reason why prevalence should not be similar. The prevalence of calcium quoted in these population studies is likely to be higher than that seen clinically due to differences in imaging methodology. This is because the imaging methods used in populations studies, such as electron beam computed tomography, are more sensitive in comparison to clinical imaging methods, such as conventional CTA and angiography(177). An additional limitation of the prevalence data is that the severity of calcification is not reported and the prevalence of more severe grades of calcification, which are of most interest in regard to complications and treatment failure, is unknown.

Moderate or severe calcification was identified in 38% of cases in a large IVUS study of the coronary arteries (9). There are no comparable studies available in the femoropopliteal arteries and there is a paucity of peripheral IVUS data on vessel calcium prevalence. Angiographic derived prevalence information from clinical trials is limited in value as many device trials explicitly exclude patients with severe calcification (2, 17). Real world registries and investigator-initiated studies generally have less narrow exclusion criteria and provide some useful data. These suggest that the prevalence of clinically significant femoropopliteal calcification may be between 35-45%(178-180), however these conclusions should be treated with caution due to variability in study designs, the risk of bias in patient selection and, perhaps most importantly, the lack of standardisation in calcium scoring.

Vascular calcification is an important negative predictor of outcomes for patients with PAD with severity of PAD and risk of amputation being increased as calcification becomes more severe(181). It is also an important predictor of outcomes for endovascular intervention in the peripheral arteries(17, 182). Calcified lesions are associated with poorer outcomes both due to

residual stenosis due to failure to dilate and severe dissection(183) and from late restenosis (184). Failure to achieve an adequate lumen after angioplasty leads to a higher rate of adjunctive stenting (185).

2.4.2 Medial and intimal calcification

Arterial calcification is commonly categorised as medial and intimal, depending on its location in the vessel wall. Although the exact mechanisms of vascular calcification are not completely elucidated it is now thought to be a complex intracellular molecular process with different processes driving the two types of calcification(17). Medial calcification (also called Mönckeberg's medial sclerosis) is associated with diabetes mellitus and chronic kidney disease(186) and is characterised by the accumulation of calcium in the media due to osteogenic differentiation of vascular smooth muscle cells(187). Intimal calcification occurs within atherosclerotic plaques due to lipid accumulation, pro-inflammatory cytokines and apoptosis(188). These processes result in osteogenic cell differentiation within the plaque(189). Intimal calcification is associated with lumen reduction due to the associated atherosclerotic plaque while medial calcification does not in itself cause obstructive disease but predisposes the vessel to atherosclerotic plaque deposition due to the reduction in wall elasticity and compliance and a loss of potential for positive remodelling(17). As long ago as 1950, Lindbom was able to differentiate between medial and intimal calcification(190), describing medial calcification as having a "regular, diffuse and fine-grained appearance" affecting the entire circumference in a widespread distribution and intimal calcification as being composed of "irregular, scattered and discrete plaques". He also noted that intimal calcification tended to encroach on the lumen whilst with medial calcium the intima was not generally thickened. These descriptions are still valid today with medial calcification often referred to as having "tram-track" appearances due to the parallel lines of the fine-grained circumferential calcium(191).

2.4.3 IVUS quantification of calcification

Quantification of vascular calcium is based on the arc of calcium using an electronic protractor centred at to the middle of the lumen. This measurement is considered to be valid to ±15° due to the variation in beam width, and lateral resolution, at different depths(25). Typically, this is used to measure the maximum calcification present. The length of calcification can be measured if mechanical pullback is used and can be estimated with manual pullback if the position of the IVUS image can be verified against fiduciary vessels, bony landmarks or a radio-opaque ruler on angiography.

It is not possible to estimate calcium volume as only the leading edge of a calcified lesion can be seen with IVUS with the rest of the lesion hidden by the acoustic shadow caused by the complete attenuation of the beam by calcium(192). It is also not possible to be certain of calcium location in

relationship to layers of the arterial wall using IVUS. This is due to inability to precisely delineate the plaque and media boundary and the shadowing artefact that obscures calcium deeper in the wall(25). The use of the terms “intimal” and “medial” is therefore not recommended for describing IVUS appearances and the preferred nomenclature for describing the position of calcium is “superficial” for calcium located in the 50% of the plaque that is closest to the lumen and as “deep” for calcium located in the 50% of the plaque further away from the lumen(25). The problems generated by the presence of calcium have resulted in guidelines for performing atheroma volume analysis in the coronary artery to recommend avoiding segments with calcification and to exclude frames with >45° arc of calcification from analysis(193).

2.4.4 Calcium and dissection

There is a clear association between vessel wall calcification and post-angioplasty dissection (194, 195). Demer (196), demonstrated in rabbits that calcified vessels required higher pressures for adequate dilation due to reduced distensibility and that calcification was associated with disruption of the vessel wall during balloon dilation. Tearing of the vessel wall occurs most often in areas where there is a marked change in the wall’s elastic properties such as at the transition from normal wall to calcium (197). Fitzgerald et al.(198), investigated dissection in the coronary arteries and found that angioplasty of vessels with homogeneous, elastic walls resulted in relatively small tears, whereas in vessels with heterogeneous walls containing calcified plaque there was more extensive dissection. They found that 74% of cases with dissection had calcification and in 87% of these cases the dissected plaque was directly adjacent to the calcium. Vogt et al.(129), confirmed with IVUS that there was a positive association between the degree of calcification and the size of post-angioplasty dissection in the peripheral vessels.

2.4.5 Calcium scoring systems

A major limitation in understanding the role of vessel wall calcium in endovascular interventions is the lack of a standardised method of grading calcium severity in the peripheral arteries. The lack of a commonly agreed scoring method in the peripheral arteries contrasts with the coronary arteries where validated and widely adopted systems such as the SYNTAX score(199) have enabled standardisation of lesion complexity grading and improved the understanding of the role of vessel calcification in coronary artery interventions.

Most studies of endovascular treatment methods report the severity of calcification in some form, although there are some studies in which calcium severity is not reported at all (2, 4). The quality of calcification reporting is highly variable ranging from very limited data, often just stating the percentage of severe calcification(3, 200, 201), to reporting of the full range of severity grades present (178, 180, 202-206). Interpretation of these results is often hampered by inadequate or non-existent explanation of the criteria used for severity grading (3, 178, 180, 200, 201, 206, 207),

with a minority of reports providing clear and complete definitions of calcium classification methodology (161, 165, 168, 204, 205, 208). Most scoring systems have been created for use in a specific study(161, 165, 168, 184) however two of the systems have been created with the aim of providing a standardised scoring method to characterise calcium(17, 162).

Most angiographic scoring systems are based on two features of vessel wall calcification: the length of the calcified lesion and the distribution of calcium around the vessel wall. Length of calcium is usually defined in terms of the absolute length but has also been defined as a percentage of the entire lesion length(162, 168). Distribution of calcium around the wall is usually defined by the number of sides of the wall with calcium present (i.e. unilateral vs. bilateral) although this may also be defined as involvement of <180° or ≥180° of the wall(162, 168). The various scoring systems categorise these two parameters into grades of increasing severity, with a variety of threshold values used to define less severe from more severe lesions. Lesion length thresholds vary from 1cm(161, 165) to 5cm(17, 208) while the two systems that use percentage of the lesion length differentiate lesions by whether calcium is present along <50% or ≥50% of the length of the lesion(162, 168).

The use of degrees of the circumference instead of unilateral or bilateral is a somewhat confusing method for defining distribution around the wall given that the planar nature of angiography cannot demonstrate the arc of the circumference. This nomenclature is also rather superfluous as these systems further define the angle criteria in terms of the number of sides of the artery containing calcium (162, 168). In most systems interpretation of calcium distribution around the wall is further hampered by a lack of clarity in image interpretation instructions, with only one system specifically defining that calcium must be present on both sides of the artery at the same location to be categorised as bilateral(162), and only one study provides guidance on the type of angiographic imaging to be used by specifically stating that imaging should be obtained with orthogonal planes(168). There is also variation in the number of grades used within the scales used by scoring systems (ranging from two(208) to five(17, 168)) and in the nomenclature used for these scales. Sometimes descriptive terms are used specifying the degree of severity for each grade(161, 162, 168, 208), but in other systems a numbered scale is provided without specifying the level of severity(17, 165).

All but one of the currently available peripheral calcium scoring systems relies solely on angiographic imaging. The exception is the system devised by Fanelli et al.(184), which combines angiographic and CTA imaging(184). The Fanelli system uses the length of calcium as assessed by angiography, using a threshold of 3cm between less severe and more severe calcification, and quadrants of the circumference containing calcium as assessed with CTA. The quadrants of calcium are used instead of the number of sides of the vessel to assess distribution around the

wall. In this system there are eight grades defined by the four possible results for quadrant of calcium and the two possible results for length.

A significant limitation of these scoring systems is the limited validation data. Fanelli et al.(184), compared combined angiography and CTA calcium grading to outcomes after DCB angioplasty and found a significant reduction in primary patency for cases with calcium in the two most severe grades (i.e. lesions with calcium present in all four quadrants). IVUS was used as a gold standard for validation of the grading system, although it was unclear how this was done and no results were provided on the degree of agreement between the CTA/angiography score and the IVUS findings(184). This study was limited by its small sample size (60 subjects) and was limited to 6-month follow-up. Tepe et al.(182), assessed the COMPLIANCE 360 method(168) and the PACSS method(17) against late lumen loss (LLL) after DCB angioplasty in 91 subjects. There was a significant increase in LLL in vessels with moderate or severe calcification according to COMPLIANCE 360 and with bilateral calcification according to PACSS (grades 3 and 4). Calcium on both sides of the artery was an independent predictor of LLL whereas calcium length was not. This study was also limited by follow-up to 6 months. Okuno, et al.(209), investigated calcification scoring using the PACSS system in patients undergoing femoropopliteal revascularisation (primarily treated with BMS), with follow-up up to 24 months. Primary patency was significantly lower while major adverse limb events and TLR were significantly higher with bilateral calcification (grades 3 and 4). Bilateral calcification was an independent predictor of loss of primary patency whereas calcium length was not. A common finding from these studies was distribution of calcium around the wall seems to be a better predictor of poor outcome than the length of calcium.

The variable number of grades used in scoring systems, the heterogeneity of thresholds used to define calcium grades, the subjective nature of the measures and the lack of clarity in regard to what constitutes severe calcification all make comparison between scoring systems difficult. A further complication is the incorporation of calcium type (i.e. intimal, medial or mixed) into one of the scoring systems(17). The heterogeneity of system design and the limited detail provided to assist interpretation also raises concerns about the reliability of these systems. The reliability of these scoring systems is unknown as there have been no reports of inter- and intra-observer agreement for any of the available systems. Reliability is a key factor in determining how well a scoring system categorises calcium severity and the lack of this type of data is another impediment to improving our understanding of the peripheral arterial calcification.

There is only one study that has used IVUS to assess the performance of calcium scoring systems. Yin, et al.(210) assessed the performance of three angiographic scoring systems (the PARC, PACSS and Definitive Ca^{++}systems(17, 161, 162)) against IVUS imaging in a subgroup of 47 patients from the Jetstream G3 Calcium study(160). All three angiographic scoring systems had

low sensitivity for the presence of calcium. IVUS identified calcium in 44 of 47 patients compared to 26 of 47 with angiography ($p<0.001$). All three systems were also found to under-measur the length of calcification. These findings are in agreement with earlier IVUS studies that have reported detection rates of calcium by angiography as low as 30% in the femoral artery(10) and 38-46% in the coronary arteries(9, 78). Angiographic assessment of calcification location (unilateral versus bilateral) did not agree well with the arc of calcification as seen on IVUS with the angiography under-estimating the arc of the vessel circumference involved.

In all three scoring systems there was a significant difference in calcium length (as measured by IVUS) between severe and none/mild grades, however only the Definitive Ca^{++} system was able to differentiate between moderate and severe calcification. None of the three scoring systems were able to differentiate between severe calcification and moderate calcification with angiographic calcium location criteria (unilateral vs bilateral) when compared to IVUS arc of calcification. Only the PARC system could differentiate between severe and mild calcification according to arc of calcification. None could differentiate moderate from mild calcification when compared with either length or arc of calcification as measured by IVUS. Overall, this analysis suggests that none of these scoring systems perform well at differentiating between mild and moderate or moderate and severe calcification.

There were some limitations to this analysis. There was no comparison between the scoring systems with analysis restricted to comparing each system with IVUS. The analysis was restricted to three of the available scoring systems and the performance of other systems is unknown. Even though the PACSS system has the capacity to classify on the basis of calcium location (intimal, medial or mixed), no comparison of this with IVUS location data was reported. The study could not validate the predictive performance of the scoring systems (or IVUS assessment) in relation to outcomes as follow-up was limited to 30 days post procedure. Inter and intra-observer agreement was not assessed for any of these scoring systems.

Assessment of calcium severity is an important component in the decision-making process when planning endovascular treatments. There is a high prevalence of calcification in peripheral arterial disease and this is a clinically significant problem. There are a variety of scoring systems available to assess calcium severity but very little validation data on how well these scores predict outcomes. The data available suggests that bilateral calcium on angiography or calcium in four quadrants on CTA may be the best predictors of poor outcome. There is no data comparing the performance of scoring systems. Comparison with IVUS suggests that angiographic systems are poor at differentiating between more severe lesions and milder lesions. It is unclear whether there are differences in reliability between scoring systems as this has not been reported for any of the available systems.

2.5 Dissection grading

The following sections review the current state of knowledge regarding IVUS detection of dissection, the clinical significance of dissection and systems for classifying dissection severity in the context of the research question: are there significant differences in IVUS anatomical parameters for severe dissection between the NHLBI and Kobayashi systems and are there differences in inter-rater reliability between the systems?

2.5.1 Dissection in peripheral arteries

Effective angioplasty involves a degree of controlled dissection as a key mechanism for achieving adequate vessel dilation is plaque fracture (27, 109-11). Dissection is extremely common after femoropopliteal angioplasty with some degree of dissection seen in 53-88% of cases with IVUS (10, 129, 211, 212) and severe dissection seen with angiography in 60-84% of cases (18, 20). Dissection is strongly associated with the presence of calcification in the vessel wall(198). Practice guidelines for peripheral practice recommend adjunctive stenting after angioplasty if there is severe dissection, although what constitutes a severe dissection is not defined (213). This is based on concerns about the risk of restenosis or thrombosis if a dissection is left untreated. Balanced against the desire to eliminate dissection by stenting is the “leave nothing behind” philosophy (214). This approach is driven by the recognition of the significant rates of ISR and re-intervention after stenting in the femoropopliteal arteries(203, 215). This is a different paradigm to the coronary arteries where the risk of thrombosis when dissection is present is considered high enough to warrant a stent first policy(194, 216-218).

There is evidence that severe dissection in the peripheral arteries results in lower primary patency rates and higher rates of TLR compared to mild dissection (19, 20), although there is also evidence that some severe dissections may be less of a risk than is usually assumed(179). The risk of leaving mild dissection untreated is much lower and outcomes for mild dissections appear to be similar to cases with no dissection(19). The ability to perform reliable and reproducible grading of dissection severity is important due to the different treatment and outcome implications of mild vs. severe dissections. The only generally accepted criteria used in clinical practice for classifying dissection severity is evidence of flow-limitation on angiography. Flow-limitation is, however, limited by being a subjective criterion with no consensus on how it should be defined. Grading systems have been developed to classify dissection (discussed in Section 2.5.4) but have not been generally adopted in clinical practice. The lack of objective methods for classifying dissection is surprising given its high incidence and the potentially serious implications of severe dissection.

2.5.2 IVUS detection of dissection

There are many possible IVUS criteria for assessing dissection severity. These include the depth of the dissection into plaque, the circumferential arc of the dissection in degrees, dissection length, residual lumen area and luminal dissection area (25). Of these the only method that has been regularly used for reporting quantification of dissection with IVUS is measurement of the arc of dissection in degrees.

Coronary studies have shown that angiography identification and classification of dissection is unreliable with angiography identifying only 38-59% of cases of dissection seen with IVUS (58, 71, 121, 219). In the peripheral arteries, Gerritsen et al.(220), reported that angiography was able to detect dissection in 92% of cases identified by IVUS. However, Van Lankeren et al.(10), found angiography detected only 52% of cases of dissection identified by IVUS. This markedly lower result may be explained by differences in analysis methodology. In the former study, analysis was restricted to the 181 IVUS images and limited to the segment of maximum stenosis. The later study used a more comprehensive and systematic technique to assess the entire treated zone for each lesion and analysed 1253 images (10, 220). They found that the mean dissection arc when dissection was not detected on angiography was 58° whereas the mean arc for dissections that were detected with angiography was 91º ($p<0.001$), suggesting that less severe dissections were most likely to be missed by angiography (10).

2.5.3 Clinical significance of IVUS-detected dissection

IVUS evidence regarding the clinical significance of IVUS detected dissection is mixed. While some coronary studies have identified dissection as a predictor of restenosis in the coronary arteries (58, 125) others have not found this to be the case (126, 127, 221). Results for peripheral artery IVUS have also been mixed. Gussenhoven et al.(26), showed that while the presence of dissection after PTA was not a predictor of treatment failure, the degree of dissection (magnitude of the arc of dissection) was positively associated with loss of patency, suggesting that that the more severe dissections are the most relevant clinically. Van der Lugt et al.(130), found that dissection was associated with lower rates of early restenosis (at one month) but with higher rates of late restenosis (at six months). The authors interpreted these seemingly contradictory findings as suggesting that the presence of dissection confirmed that adequate dilation and vessel stretching had occurred during angioplasty resulting in good initial result, however dissection also suggested that there had been greater barotrauma and that this may result in a greater inflammatory reaction leading to more aggressive NIH and hence higher restenosis rates later. There is currently no data available on whether there is a specific threshold of arc of dissection can be used to guide the need for further treatment once dissection has been detected.

2.5.4 Dissection classification

Guidelines recommend adjunctive stenting when angioplasty results are unsatisfactory but do not clearly define what severity of dissection requires adjunctive stenting (40, 213, 222). It is common for studies in the peripheral arteries to dichotomise dissection by the subjective criteria of flow-limiting vs. non-flow limiting(4, 165, 207, 208).

The clinical importance of post-angioplasty dissection was evident from the earliest days of coronary angioplasty(76, 216, 223). The NHLBI classification system was created to provide a standardised method of grading severity of coronary artery dissection and has been validated against clinical outcomes (224, 225). It has six grades of severity categorised by specific patterns of dissection appearance. As there is no grade allocated to vessels with no dissection, there are in fact seven potential classifications with this system. Assessment by an adjudicating core laboratory in a large coronary artery RCT assessed inter- and intra-observer agreement for the NHLBI classification and found good inter- observer agreement for the presence of dissection (k=0.75) and moderate agreement for grading of dissections (k=0.66). Intra-observer agreement was lower for presence/absence of dissection for both assessors (assessor one k=0.60 and assessor two k=0.58) and lowest for grading of dissection (k=0.48 and k=0.51) (226).

Until recently the NHLBI classification has been the only dissection grading system available and has therefore been used in peripheral arterial device trials that have applied a dissection grading system (2, 179, 180). Recently a modified version of the NHLBI system was validated against clinical outcomes in the femoropopliteal arteries, with Kaplan-Meier analysis confirming that severe dissection (type C-F) had a significantly reduced primary patency ($p<0.001$) and increased TLR rate ($p<0.001$) compared with mild dissection (type A and B) after plain angioplasty(20).

A limitation of the NHLBI classification system is the lack of reproducibility and reliability data in the peripheral arteries. The differences between the coronary and peripheral arteries, particularly the greater length, complexity and calcification found in the peripheral arteries, are such that it cannot be assumed that this system performs reliably in the femoropopliteal arteries. This system is effectively used as a dichotomised classification with dissections being classified as either mild (no further treatment) or severe (requiring treatment) (20, 179, 180). There is a degree of variation in where the threshold level between mild and severe as been set, with severe dissection usually being defined as Type C or greater (2, 179) and at other times as Type D or greater (180).There is no data on how performance of the NHLBI system changes depending on where this threshold is set.

Kobayashi et al.(19), have recently published a peripheral artery specific dissection classification using a simplified grading system designed specifically for use in the femoropopliteal arteries. The

key features in this system are the small number of grading options (two grades of dissection and a third grade for no dissection) and the simplicity of the differentiation between mild and severe dissection, with mild dissection defined as having a width of <1/3 of the lumen and a severe dissection having a width of ≥1/3 of the lumen. This is simpler than the NHLBI classification, which has seven potential options available, and is based on a series of patterns that the user is required to understand. This system has been validated for primary patency with severe lesions having significantly poorer long-term patency at up to three years ($p<0.001$). This system has excellent inter-observer agreement for no dissection ($k=0.983$), mild dissection ($k=0.918$) and severe dissection ($k=0.961$). These results are much better than for agreement testing of NHLBI classification(226). This suggests that the simplified Kobayashi classification may be more reliable, however the NHLBI reliability results were from use in the coronary arteries and comparison for results in different systems may not be valid. Intra-observer agreement was not reported for the Kobayashi classification and no comparison is possible for this parameter. The relative performance of the NHLBI and Kobayashi classification systems at predicting outcomes for mild and severe dissection has not been performed nor has agreement been tested in the same group of patients. Comparison against IVUS imaging would be useful to help establish if the two classification systems are classifying the same lesions into mild or severe groups.

The established method for assessing dissection severity with IVUS is the measurement of the arc of the dissection, in degrees, from the base of the dissection (the point where the dissected plaque separates from the vessel wall) to the free tip of the dissection with the centre of the arc being the centre of the vessel(25, 26). This method is relatively simple to perform and produces a single measurement parameter allowing for easy comparison of results. The reproducibility of IVUS arc measurements of calcification in the coronary arteries is good (ICC=0.78)(227) but there is no data for dissection arc measured in degrees. The inter-observer agreement of IVUS dissection assessment has been investigated in the peripheral arteries for a semi-quantitative method (dissection graded by the number of hours of a clock face) and found good agreement between observers ($k=0.69$, total percentage of agreement=85%) (67).

A limitation of arc of dissection assessment is that it only assesses one property of a dissection. It is unclear whether this is the most important parameter or whether there are other parameters that better define the severity of a dissection. Other dissection properties include the residual lumen area, the dissection lumen area and the area of the dissected plaque. Of these parameters residual lumen narrowing, assessed using angiography, has been shown to be associated with slow flow and the risk of early thrombosis and occlusion in the coronary arteries(218). Lumen narrowing is the prime determinant of mild and severe dissection in the Kobayashi dissection classification(19) and although the NHLBI classification does not directly assess the degree of residual lumen narrowing it is implied in the criteria definitions(20, 224).

A problem with lumen measurement in the presence of dissection is defining what constitutes the lumen to be measured. After dissection, there are usually two inter-connected spaces: the original lumen (usually increased in size) and a space between the dissected flap of plaque and the vessel wall. It is not always clear what has been measured when lumen area is reported, although some investigators clearly identify the new space created deep to the plaque with the use of the term “neolumen”(27, 198) or indicate that this space has been excluded by using the terms “free” or “true’ lumen(26, 49, 56, 67, 128, 211, 212). It is likely that the “neolumen” is not viable lumen as it often obliterated by thrombus formation neointimal hyperplasia (228, 229) and while it is likely that most investigators have excluded it on the assumption that it will not contribute to effective flow, this is often not explicitly stated. The relationship between the arc of dissection and the degree of lumen narrowing has not been reported.

Dissection flap area may also be a useful parameter for assessing dissection severity as larger areas of atheroma protruding into the lumen are likely to obstruct more of the lumen. Atheroma area has been shown to be a predictor of hematoma for stent-edge dissection in the coronary arteries(230) but there is no data on how this relates to lumen area or restenosis after angioplasty.

Dissection is a significant problem in peripheral endovascular treatment. There is a lack of clarity and considerably heterogeneity in how dissection is classified. There are two angiographic classification systems currently available but there is limited validation of these in the peripheral arteries and no comparative data as to superiority of one over the other. There is also limited reliability data for dissection classifications when used in the peripheral arteries and no comparative data for reliability between the NHLBI and Kobayashi classifications in the peripheral arteries. There are no studies that have used IVUS to assess the performance of angiographic dissection classification systems.

2.6 Core laboratory analysis of peripheral arterial IVUS

In this section the current state of knowledge regarding IVUS-based atheroma volume estimation using core laboratory analysis is reviewed in the context of the research question: how many cases undergoing IVUS during peripheral endovascular intervention have an adequate proportion of suitable images for performing atheroma volume analysis?

IVUS core laboratories are used extensively in coronary device trials for the adjudication of imaging findings. Analysis of IVUS data to generate volumetric data of atheroma by core laboratories has been used in coronary applications for studies of anti-atherogenic medications(193, 231). In these studies, a segment of the coronary artery is carefully selected prior to analysis to ensure high image quality and causes of reduced image quality, particularly calcification, are actively excluded(231). IVUS based atheroma volume analysis using core

laboratory analysis methods has been used to compare the plaque burden in the coronary and tibial arteries(22) and to assess effectiveness of atherectomy for the removal of atheroma (21, 23).

Calcification is a major limitation for imaging the wall structures with IVUS and measurement of the EEM area(25), which is essential for volume estimation, becomes unreliable once more than 45° of the wall is obscured by calcium(193, 231). The high prevalence and extensive nature of calcification in the peripheral arteries suggests this may be a problem if volumetric analysis of atheroma is attempted over the length of the entire lesion.

The TRUE study reported the use of IVUS based plaque volume estimation to assess the amount of tissue removed by a rotational atherectomy device(21). In this study, mechanical pullback was performed before and after atherectomy of lesions in the SFA, popliteal artery and tibio-peroneal trunk of 18 patients. A significant reduction in atheroma volume after atherectomy was reported with a mean decrease of 56mm^3 (479.8mm^3 prior to treatment and 423.2mm^3 after treatment, $p<0.0001$) resulting in a lumen gain of 64.2mm^3. The gain in MLA after treatment was not reported. The prevalence and extent of calcification was not also reported.

The TRUTH study used IVUS volumetric analysis of IVUS imaging to assess the performance of an orbital atherectomy device(23) in 25 patients with stenotic or occlusion lesions in the SFA, popliteal or tibioperoneal trunk. IVUS showed that there was a small increase in MLA after atherectomy (from 4.0mm^2 to 4.7mm^2, $p=0.55$) but that the significant lumen gain was achieved by angioplasty (from 4.7mm^2 to 9.1 mm^2, $p=0.026$). Atheroma volume analysis was performed and found that there was no change in mean lumen area over the entire lesion after atherectomy (22.1mm^3/mm before and after atherectomy). The median arc of calcification for lesions included in this study was 137° with an interquartile range (IQR) of 96° to 205°. No information was provided on whether the presence of calcium limited volumetric analysis.

Yin et al.(22), used IVUS core laboratory analysis to assess atheroma characteristics in 42 tibial or peroneal lesions and 79 matched coronary lesions. They found the tibial and peroneal arteries to have smaller vessel and atheroma volumes (6.0mm^3/mm vs. 7.0mm^3/m, $p=0.008$) than coronary arteries but similar percent atheroma volumes (64.3% vs. 59.7%, $p=0.56$). Calcification was more severe in the tibial and peroneal arteries with a maximum calcium arc of 285° compared to 81° in the coronary arteries ($p<0.001$). No information was provided on whether the presence of calcium limited volumetric analysis.

In the TRUE study (21), half of the potential cases were excluded due to calcification limiting the technical quality of the IVUS imaging. In addition, analysis was performed in a 20mm segment (representing a third of the total IVUS pullback) that was selected on the basis of less severe disease and segments with more severe disease were avoided due to reduced technical quality of

the pullback through these segments. This suggests that a substantial, but undefined, proportion of frames in an IVUS pullback were likely to be compromised by poor image quality caused by severe disease including calcification. The study of Yin et al.(22), did not address how calcium effected the analysis of the IVUS imaging. Quantitative atheroma results were reported for all cases, however extensive calcification (median arc of calcification of 285°) was also reported but there was no information on how this affected the ability to obtain atheroma measurements. Similar analysis methods were described by Babaev et al.(23), and again no information on how calcification seen in this study (median arc of 137°) affected the atheroma volume was presented.

There is limited data specifically addressing whether peripheral artery IVUS, obtained during endovascular interventional procedures, is of sufficient quality to allow accurate volumetric estimation of atheroma volume. The few reports from studies that have attempted IVUS-based volume estimation in peripheral arteries either did not address the potential technical limitations at all or have provided very limited information. The TRUE study results suggest that calcium may have excluded a large proportion of cases from analysis and that analysis, when possible, could only be performed in selected segments rather than the entire lesion. Give that atherectomy may be less effective in hard calcified parts of a lesion, the selective nature of this analysis could result in less generalizable results that may over-estimate the effectiveness of plaque removal by atherectomy.

There is also the possibility that a different, presumably less strict, threshold for excluding frames from analysis was used in some of these studies compared to what is conventionally used in coronary artery atheroma regression studies. Due to the lack of information this remains conjecture.

Current understanding of how calcium affects IVUS imaging suggests that calcium may severely limit the ability of IVUS to accurately measure the EEM. Without this measurement IVUS images cannot be used to estimation atheroma volume. The magnitude of this problem is not clear, although a small study comparing MRI and IVUS imaging in the SFA found that EEM measurements could not be obtained in almost half of the IVUS images(24). Further studies are required to investigate what proportion of images acquired during IVUS scans are not suitable for analysis. This information is required before attempting to use IVUS to assess atheroma volume in the peripheral arteries.

2.7 Conclusions

There is extensive evidence of the high accuracy and reliability of IVUS imaging to characterise the features of normal and abnormal vessel. IVUS has been shown to be superior to angiography for characterising disease severity. IVUS has been used to assess treatment with all the current

available treatment technologies currently used in endovascular interventions. Evidence from the coronary and peripheral arteries suggests that the use of IVUS may improve outcomes of endovascular interventions however studies in the peripheral arteries are all retrospective and all have significant methodological limitations. Prospective data is required to assess whether the use of IVUS can indeed improve outcomes.

Calcification is highly prevalent in the peripheral arteries and is associated with poorer outcomes for endovascular interventions. There is a good deal of evidence that IVUS is a more sensitive diagnostic tool for detecting and characterising vascular wall calcification. There are multiple scoring systems for grading calcium severity, almost all of which are angiography-based. There is little data using IVUS to assess how well these systems categorise lesions by severity of calcification. There is also no data comparing the performance of these scoring systems and no data on the reliability of calcium grading.

Dissection is a major complication of endovascular intervention associated with poor clinical outcomes. There are two dissection classifications currently used in the peripheral arteries. There are no studies reporting the use of IVUS to assess these classifications systems. There are no studies of the comparative performance of the two systems and also no studies comparing their reliability.

While the use of core laboratory analysis methods is commonplace in the coronary arteries, the use of this form of analysis has rarely been reported in the peripheral arteries. Accurate estimation of atheroma volume with IVUS could assist in understanding the role of atheroma burden in the PAD and the effectiveness of atherectomy techniques for atheroma removal. Although volumetric analysis of atheroma burden has been reported in the peripheral arteries it is not clear whether the more extensive calcium present in these vessels affects the acquisition of the measurements on which this analysis is based.

IVUS imaging produces excellent quality imaging of the peripheral arteries and has provided numerous insights into current treatment methods. The value of IVUS as a research tool is well recognised, however the role of IVUS in standard clinical practice is still unclear. Almost 30 years after it was first used in the peripheral arteries, it is still unclear whether the use of IVUS as an adjunct to angiography results in better outcomes for patients being treated for disease in the femoropopliteal arteries. There is some evidence to suggest that there may be a benefit from the use of IVUS however this is all retrospective, and there is no prospective, randomised data available to allow more definitive conclusions to be reached. This information is required before IVUS can to be used in a more routine, systematic manner.

3 THE IMPACT OF INTRAVASCULAR ULTRASOUND ON OUTCOMES OF ENDOVASCULAR TREATMENT OF FEMOROPOPLITEAL DISEASE: METHODS

3.1 Study aims, research question and hypothesis

3.1.1 Study aims

The aims of this study were to investigate whether femoropopliteal artery interventions using combined IVUS and angiographic imaging guidance results in a lower rate of binary restenosis within 12 months for participants with severe claudication or CLI compared to interventions utilising angiography only, and to quantify how often and in what ways IVUS changes the endovascular treatment performed.

3.1.2 Research questions

This chapter will present the methods used to investigate the following research question related to the aims stated in section 3.1.1.

Research question 1 (RQ1): Will the addition of IVUS imaging to femoropopliteal artery endovascular interventions result in a reduction in binary restenosis within 12 months in participants being treated for severe claudication and CLI?

3.1.3 Hypothesis

The hypotheses related to the aims and research questions were:

Hypothesis 1: that interventional procedures using combined IVUS and angiographic imaging will have a lower rate of binary restenosis within 12 months compared to interventions using angiography alone.

3.2 Justification of the study design

This was a single centre, balanced randomisation (1:1), non-blinded, parallel-group study conducted in South Australia. Participants were randomly allocated into 2 parallel groups. The control group had interventional treatment based on the angiographic imaging and the treatment group had interventional treatment based on a combination of IVUS and angiographic imaging. The basic design of the study is illustrated in the flow diagram below (Figure 3.1). Participants were followed for a minimum of one year with regular clinical and imaging surveillance with the primary outcome being freedom from binary restenosis. This study is registered with Australian New Zealand Clinical Trials Register (Trial ID: ACTRN12614000006640)(232).

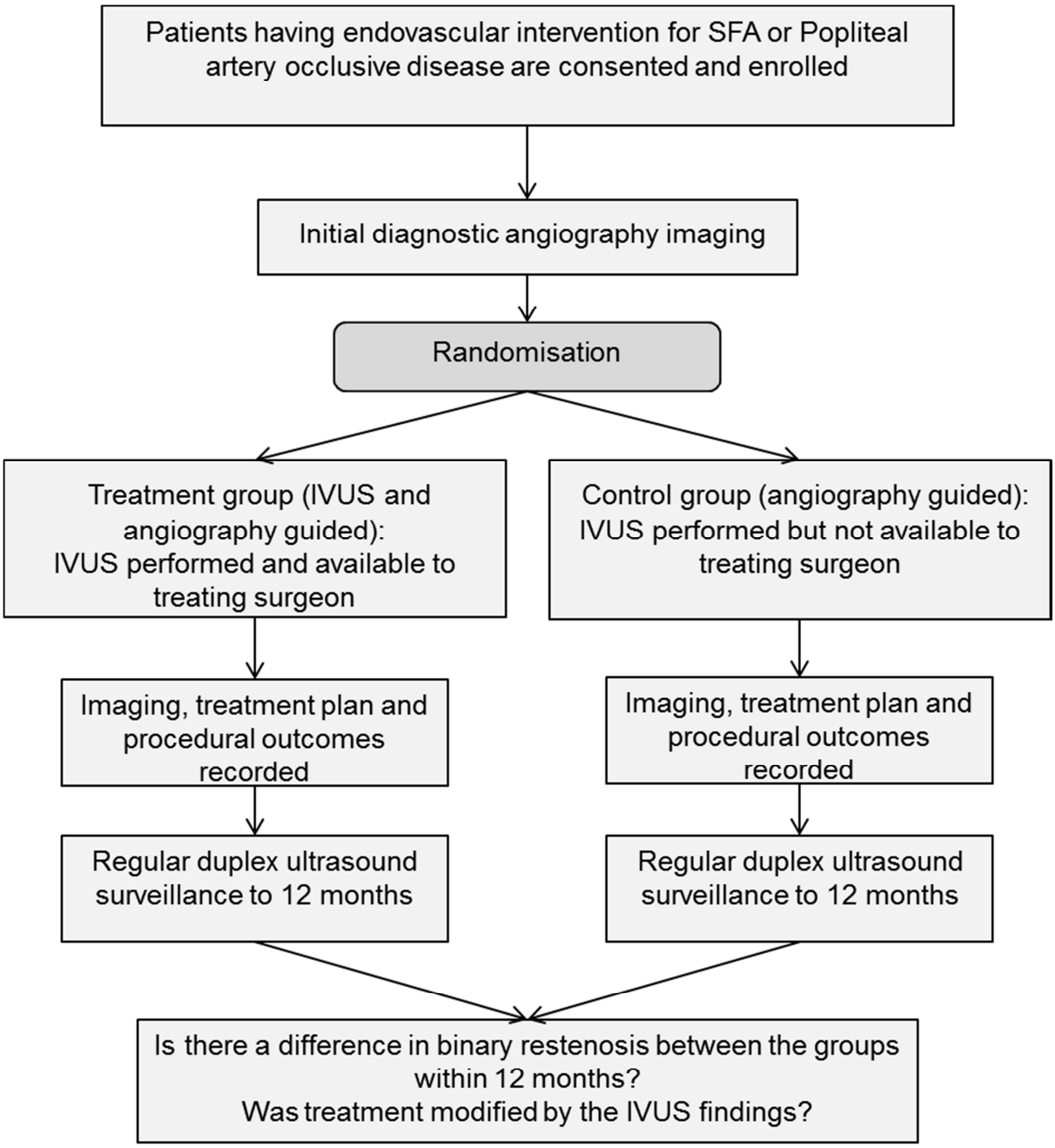

Figure 3.1 Flow diagram of basic study design

There is retrospective evidence that the use IVUS may confer clinical outcome benefits for peripheral endovascular interventions. Higher level evidence to justify the additional time and cost of adding IVUS to standard practice is currently not available. The lack of this level of evidence represents a significant gap in our understanding of the role of IVUS in peripheral interventions. Randomised controlled trial (RCT) was chosen as the study methodology to investigate the primary hypothesis as this was considered to provide the highest level of evidence for a single study investigating alternative treatment methods (233-235). The provision of prospective data was necessary to allow an evidence-based approach to the formulation of guidelines for the use of

IVUS. Alternative study methodologies such as a historical control trial, while easier to perform, were rejected due to the potential for bias from differences in practice during the time of treatment during the historical group and the increased risk of confounding variables due to differences between the two groups that might not be recognised (236, 237). The CONSORT recommendations were applied in the design of the RCT design(238). In addition, the timing of randomisation and the collection of treatment plan information after angiographic imaging allowed the collection of information on changes to the treatment plan due to information provided by IVUS.

3.3 Study population and eligibility

Participants were recruited from patients referred to Department of Vascular and Endovascular Surgery at Flinders Medical Centre from the Southern Adelaide Local Health Network catchment. Patients were eligible to participate in the study if they: 1) presented with severe life-style limiting intermittent claudication (Rutherford classification 3), defined in this unit as pain free walking distance of <200m, or CLI (Rutherford classification 4-6)(239), defined as ischemic rest pain or ulceration with evidence of arterial insufficiency of the affected lower limb, 2) had imaging evidence of a stenotic or occlusive lesion in the SFA or popliteal artery, and 3) were scheduled for an endovascular interventional procedure at Flinders Medical Centre with one of the unit's vascular surgeons.

Patients were ineligible to participate if they: (1) were unable to give informed consent due to language difficulties, or physical and/or mental incapacity, (2) were under 18 years of age, (3) had an allergy to iodine-based contrast media, or (4) had a very short life expectancy (<6 months).

3.4 Ethical oversight, recruitment and informed consent

This study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC), **453.13 - HREC/13/SAC/296** in accordance with the "National Statement on Ethical Conduct in Human Research (2007)(240). Ethical oversight of the study was performed by the SAC HREC with regular reporting of progress required over the course of the study.

Recruitment into the study occurred prior to endovascular treatment and after the decision was made to perform endovascular treatment. This was usually in the hospital outpatient clinic or on the hospital ward, if the participant was admitted to the hospital prior to undergoing endovascular intervention. Eligibility criteria were assessed and potential participants who met the eligibility criteria were provided with a SAC HREC approved information sheet that provided information of the purpose of the study. A careful verbal explanation was given, including a detailed description of the procedures that would be undertaken and an opportunity for the participant to ask questions. Participants were then asked if they were willing to be involved and, after gaining verbal informed

consent, written consent was obtained using the SAC HREC approved consent form. This form was then filed permanently in the participant's hospital medical record.

3.5 Randomisation

A web based random number generator utilising atmospheric noise (RANDOM.ORG at https://www.random.org/) was used to generate 150 random numbers. These were placed into individual sealed envelopes by a staff member not involved in the study. Randomisation occurred during the endovascular procedure after the initial diagnostic angiography imaging had been completed and after the surgeon had defined their treatment plan. Randomisation was performed at this point, rather than at the initial booking, to ensure that the surgeon's treatment plan was based solely on the angiographic information without knowledge of whether they would also have access to the IVUS imaging. Randomisation was not performed earlier in the process, such as at the time of booking, to eliminate the chance that the treating surgeon would become aware of the randomisation. Odd numbers indicated allocation to the control group and even numbers indicated allocation to the treatment group thereby generating a 1:1 allocation ratio.

3.5.1 Blinding

Blinding of the treating surgeon or the patient to the randomisation was not possible as it was impossible for the surgeon not to know if IVUS imaging was available to them during the procedure. This information could not easily be withheld from the participant as in most cases they were awake during the procedure. IVUS imaging was acquired in all cases to enable acquisition of IVUS data from all cases and so maximise the number of cases with IVUS data available for later analysis. In cases allocated to the control group the IVUS imaging was withheld from the surgeon by disconnecting the video feed to the angiography machine's monitors and ensuring that the IVUS machine display could not be viewed. No other information regarding the IVUS imaging was provided to the surgeon during cases allocated to the control group. The treating surgeon remained blinded to the IVUS imaging findings during the follow-up period, with IVUS data for cases in the control group securely stored and not accessible by the treating surgeon, to ensure that this information could not influence decisions during clinical follow-up. No attempts were made to access this information during or after the procedure.

3.5.2 Sample size

The main research question regarding differences in percentage of cases that remain free of binary restenosis within 12 months, between treatment and control group was to be addressed utilising survival analysis. With this in mind, the required sample size was estimated using Log-rank tests subroutine (241) available in PASS (242) sample size estimation software. An overall sample size of 117 subjects (58 in the control group and 59 in the treatment group) was calculated

to achieve 80% power at a 0.05 significance level to detect a hazard ratio of 0.51 when the proportion with event free survival in the control group is 0.5. The hazard ratio was set at 0.51 because evidence available from coronary and peripheral studies suggested that the use of IVUS may result in a reduction in the rate of restenosis of 50% (14, 143, 243). The estimations assumed that the study would last for four years of which subject accrual (entry) would occur in the first 3 three years, that all subjects would have at least one-year follow-up and that accrual pattern across time periods would be uniform (all periods equal). The hypothesised proportion of cases that do not develop restenosis within one year in the control group was 0.50, which was in line with the reported combined literature for angioplasty and stenting(203, 204). The hypothesised proportion of cases that do not develop restenosis within one year in the treatment (IVUS and angiography) group was 0.7. Due to the lack of data in peripheral vascular arteries this estimate was generated from results in the coronary artery literature. This evidence is quite mixed and is in a different circulation with different anatomy and haemodynamics, and more focal lesions(243, 244). For this reason, the estimated effect of the use of IVUS was set at the lower end of that stated in the literature. The sample size approved for recruitment in this study was overestimated by 25% to accommodate anticipated missing data (based on local experience for death rate and loss to follow-up) resulting in the potential for 74 subjects to be enrolled in each arm of the trial, if required. Vascular surgery unit workload data at the time of study design indicated that at least 50 patients with suitable lesions were seen yearly suggesting that the estimated sample size was achievable over a 3-year recruiting period.

3.5.3 Integration of randomisation into the endovascular procedure

As the intention of this study was to investigate the effect of IVUS when used in everyday clinical practice, no changes were made to the standard endovascular protocols used by the Department of Vascular and Endovascular Surgery except for the addition of the IVUS imaging and the randomisation process..Angiographic and IVUS imaging was attempted in all cases prior to endovascular intervention being undertaken. As stated in above, randomisation occurred after the initial angiographic imaging had been obtained and assessed. At this stage, the surgeon was required to state the treatment plan and the details of this were recorded. If the case was randomised to the control group, IVUS imaging was performed but not provided to the surgeon. In cases randomised to the treatment group, the IVUS imaging was performed and viewed by the surgeon. The surgeon was required at this point to restate their treatment plan, including any changes to the plan due to information from the IVUS imaging. These changes included an increase or decrease in the size of the balloon or stent used, an increase or decrease in the length of the treatment zone or a change in the treatment technique used. The details of any changes at this stage were then recorded. Both angiography and IVUS were performed at completion of the treatment to assess technical success. Access to the IVUS image at completion followed the same

procedure as pre-treatment imaging with IVUS available to the surgeon in the treatment group and withheld in the control group. The findings at this stage and details of any additional treatments required due to this imaging were recorded.

3.6 Angiographic procedural and imaging technique

All the endovascular interventions were performed by consultant vascular surgeons with training and experience in endovascular procedures. Angiography was performed using a GE Innova (GE Healthcare, Little Chalfont, Buckinghamshire, UK) floor mounted angiographic imaging system. A 100cm radiopaque ruler was used to locate segments of vessel to allow direct comparison between angiography and IVUS.

Arterial access to the CFA was obtained under direct ultrasound guidance. Either antegrade, ipsilateral or retrograde, contralateral access was used depending on the proximity of the lesion to the CFA bifurcation and the disease state of the aorto-iliac arterial segments. Access sheath size ranged from 5F to 7F and was determined by the sheath size required for the preferred treatment device.

In most cases imaging was obtained using hand injection of contrast. Automated injection using a pump was only performed if diagnostic images of the aorto-iliac arteries were required. In many cases computed tomography angiography (CTA), including the aorto-iliac segments, had been obtained prior to the intervention and diagnostic images of these segments were not required during the procedure. Infra-inguinal artery angiography was exclusively performed using hand-held injection. Contrast was usually given as a 10ml bolus of 50% contrast diluted with saline with different levels of contrast dilution used on some occasions at the surgeon's discretion.

Preliminary diagnostic angiography was performed in all cases prior to treatment, consisting of runs of multiple images sequentially obtained after contrast injection including wash-in and wash-out of the contrast bolus through the vessel under examination. Angiographic imaging was obtained for the CFA, SFA, PFA, popliteal artery and infra-popliteal arteries. Treatment was performed under fluoroscopic control with additional angiographic imaging runs performed as required. At the end of the treatment, completion angiography was performed in the same manner as the initial diagnostic imaging. Multi-planar images were acquired at the surgeons' discretion and were not routinely required according to unit procedural protocols.

Treatment of other vessels during the procedure was not an exclusion criterion for the study. If multiple vessels were treated within the same procedure this was always performed in proximal to distal sequence, i.e. the most proximal lesion treated first and the most distal lesion last.

The angiographic images were stored on the hospital PACS (Picture Archiving and

Communication System) (Vue PACS version 11.4, Carestream Australia Pty, East Melbourne, Australia) in Digital Imaging and Communication in Medicine 3.0 (DICOM3) format files.

The treatment method was at the discretion of the surgeon performing the procedure. The initial angiographic images were assessed and the presence of a >50% stenosis or occlusion was confirmed before proceeding with treatment. Treatment technologies available included plain balloon angioplasty (POBA), DCB, BMS, covered stent, drug-eluding stent (DES) and atherectomy (both rotational and directional). DCB therapy was always preceded by pre-dilation by POBA rather than as a stand-alone treatment. Stenting could be used as the primary therapy or as a secondary treatment (adjunctive or “bail-out” stenting) after initial angioplasty. Atherectomy was never used as a stand-alone therapy and was always used in conjunction with other therapies, most commonly with DCB angioplasty. Pre-dilatation with POBA for at least two minutes was always performed before the use of DCB. DCB inflation was for a minimum of one minute. Balloons and stents were sized at a ratio of 1:1 to 1.1:1 as per manufacturer instructions for use (245-251). In the control group, sizing was based on the angiographic reference vessel diameter (RVD) obtained using the angiography systems QVA software. In the treatment group, sizing was based on the angiographic QVA RVD and/or the IVUS RVD measurements. The length of the treatment zone was defined from the angiographic images in the control group and from the angiographic and/or IVUS images in the treatment group. Treatment success was defined as final vessel lumen with residual stenosis <30% and no flow-limiting dissection.

Anticoagulation with warfarin was ceased 5 days prior to the procedure if prescribed for management of AF but was maintained or replaced with bridging clexane therapy for higher risk indications such as mechanical heart valves and DVT. At the beginning of the procedure participants were routinely given 5000 units of heparin with additional heparin during the procedure as required. Activated clotting time monitoring was not routinely performed. At completion of the procedure participants were given a loading dose of 300mg of aspirin and 300mg of clopidogrel. Participants were prescribed life-long aspirin (100mg daily) and a one month course of clopidogrel (75mg daily). Participants were advised to continue life-long clopidogrel therapy however the duration of initial dosage was limited to one month due to hospital prescribing rules. Clopidogrel beyond this time was dependent on the patient paying as government and health insurance funding for this medication is not available for PAD in Australia.

3.7 IVUS image acquisition

3.7.1 IVUS equipment

IVUS was performed using a Boston Scientific iLab2 IVUS system (Boston Scientific, Marlborough, Massachusetts) in the first nine cases and a Volcano s5 IVUS system (Volcano Philips Healthcare,

San Diego, California) for all subsequent cases. This was due to a change in system availability. Endovascular procedures undertaken by the Department of Vascular and Endovascular Surgery were performed in angiography facility shared with the Department of Cardiology and initially access to IVUS was achieved by using a Boston Scientific system provided by Cardiology. The requirement to share the system resulted in non-availability of IVUS during two cases and the unit therefore acquired its own Volcano system that was used exclusively from the 10th case onwards.

In cases using the Boston Scientific iLab2 system, images were acquired with the Atlantis 0.018 rotating mechanical IVUS catheter, supported by a 0.018in guidewire with a minimum access sheath size of 5F. For cases using the Volcano s5 system, images were acquired with either an Eagle Eye 0.014 (supported on a 0.014in guidewire with minimum sheath of 5F) or a PV018 (supported on a 0.014in guidewire with minimum sheath of 6F) solid state phased array IVUS catheter. Choice between the latter two catheters was based on surgeon preference, based on the optimal guidewire for the planned treatment.

IVUS imaging was able to be obtained prior to treatment in cases with CTO after successful crossing of the occlusion by luminal or sub-intimal paths. This was possible in all cases of CTO without damage to the IVUS catheter.

3.7.2 Pullback technique

Mechanical pullback was used in 17 cases and manual pullback in 90 cases. Mechanical pullback was performed in all nine cases with the Boston Scientific machine (due to observed device failures in cases prior to commencement of the trial when attempting manual pullback with a rotating transducer). Mechanical pullback was performed in eight of the 98 cases using the Volcano system. Manual pullback was generally preferred with the Volcano as it allowed easier acquisition of pullbacks of lengths greater then 100mm (without the risk of device failure) and was less time-consuming than the mechanical method, and therefore more easily integrated into standard endovascular practice. Prior to using the Volcano transducer in the trial, a manual pullback method was developed that allowed long vessel segments to be imaged in a time efficient manner while still producing high quality imaging data. This involved a steady rate of manual pullback under fluoroscopic imaging and bookmarking of frames at set distances based on the transducer position relative to the radio-opaque ruler (Figure 3.2). A more detailed description of IVUS acquisition pullback techniques is provided in Appendix 3.

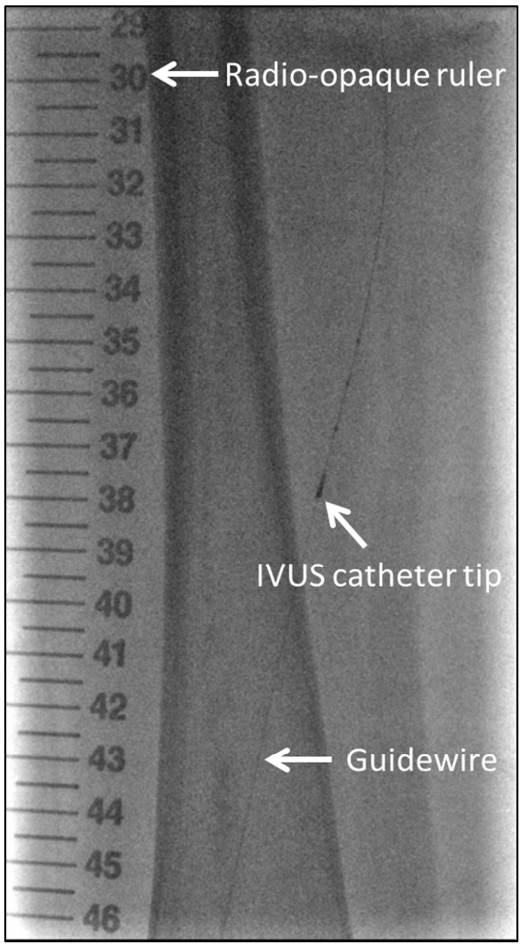

Figure 3.2 Fluoroscopy image of IVUS catheter within the SFA with radio-opaque ruler

3.7.3 IVUS image optimisation

In all cases the smallest field of view that allowed inclusion of the entire vessel was chosen. In practical terms this resulted in the diameter of the field of view being approximately twice the maximum vessel EEM diameter because of the propensity for the guidewire and catheter to be eccentrically placed against the vessel wall (Figure 3.3).

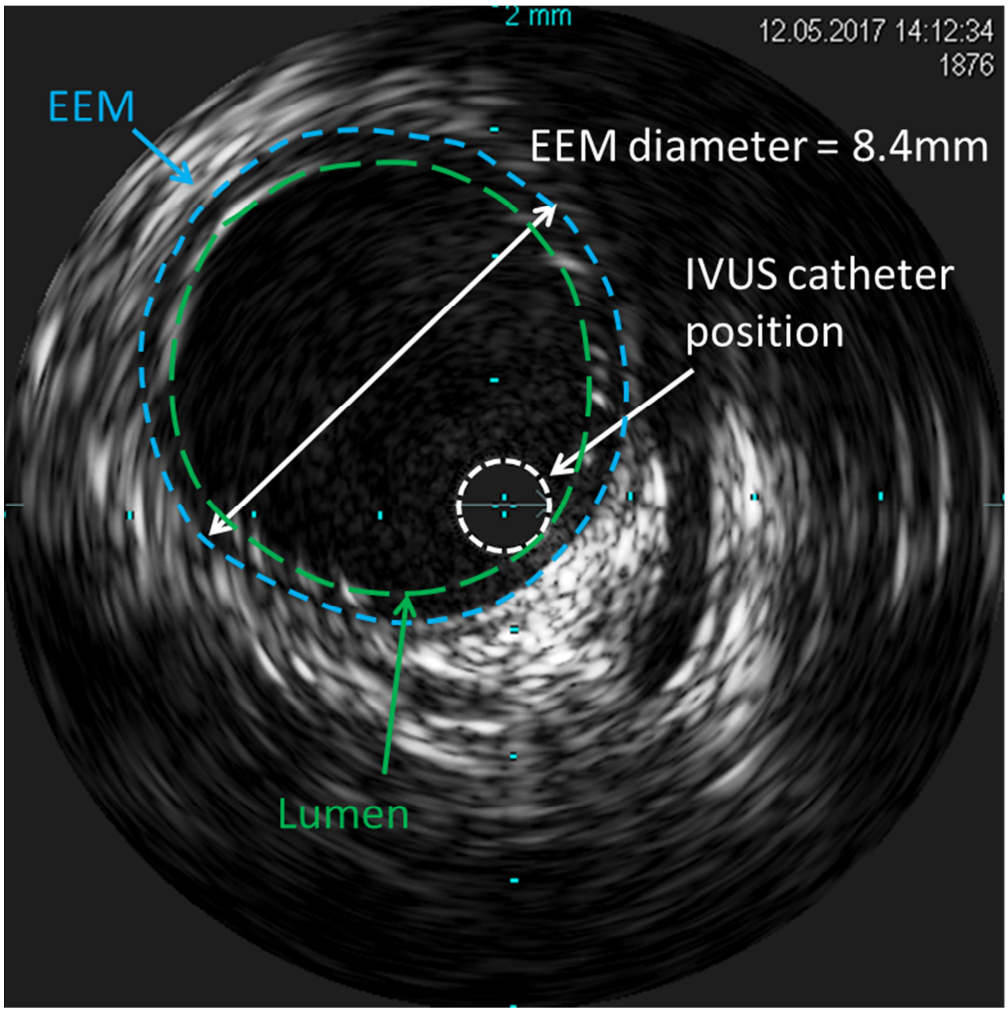

Figure 3.3 IVUS catheter eccentrically positioned against the vessel wall requiring a field of view of 16mm to ensure inclusion of entire SFA within the IVUS image

The frame rate was always set to maximum and the gain settings were adjusted for each case to ensure that all soft tissue echoes had adequate levels of brightness to be identified above the background noise level without reaching saturation.

VH was not routinely used as this would have required restriction of imaging to the Eagle Eye transducer and a field of view of 10mm. ChromaFlo (a signal tracking function that displays moving blood) was generally not used as it was found to obscure important features and impede accurate vessel wall measurement.

IVUS pullback acquisitions were analysed at the time of the procedure using the review software on the IVUS control module (iLab for Boston Scientific catheters and s5 for Volcano catheters). Images of interest were identified and diameter and area measurements obtained. Pullback acquisitions and saved still images were transferred to a DVD as a set of DICOM3 files at the end of the procedure and were archived to allow later analysis.

3.8 Angiographic measurements

Angiographic measurements were obtained using the angiography system's proprietary QVA software, as per standard department practice. Measurements were performed in normal appearing segments of the artery proximal and distal to the lesion. Proximal and distal reference vessel diameters (RVD) were obtained within these normal segments and measured in mm. The larger of the two measurements was used as the RVD for the case.

Lesion length (mm) was also measured using the QVA software, using the visual assessment of the proximal and distal edge of the lesion as the maximum extent of disease. If lesions were too long to be assessed on one image, the measurement was calculated from more than one set of images, using a combination of the ruler, bony structures and branching vessels as landmarks for ensuring accurate measurement.

3.8.1 QVA software calibration

Calibration of QVA software was required to enable accurate and reproducible measurements due to the magnification effect inherent in radiographic imaging. QVA calibration was performed by inputting a standard artery to table distance into the software for each measurement. A set of previously defined standard artery to table distances were used for calibration in each segment of the femoropopliteal artery (Table 3.1). Results of phantom testing of the artery to table top method of calibration had previously found a maximum error of ±0.2mm when applied to a 6mm SFA or 5mm popliteal artery. A detailed description of how these distances were obtained is provided in Appendix 4.

This calibration method was preferred to calibration by a sheath of known calibre (as is commonly used in PCI) as the latter method assumes the lesion and sheath are in the same plane. This assumption is commonly violated in the femoral artery where there is often a significant distance separating the sheath and the segment of interest, particularly in cases with longer lesions. This is due to the change in position of the artery along its length as it courses distally in the thigh. This can result in the artery in the adductor canal segment being 6-10 cm posterior to its position at the CFA bifurcation, with the potential for a significant difference between calculated and actual measurements. Calibrating directly to the radio-opaque ruler was not used as, although simple, it has previously been shown to result in a sizable under-estimation of vessel size(41).

Table 3.1 Standard artery to table top distances used for QVA calibration

Standard artery to table top proximal SFA (cm)	Standard artery to table top distal SFA (cm)	Standard artery to table top popliteal artery P1 segment (cm)	Standard artery to table top popliteal artery at knee joint (cm)
16.0	10.0	7.5	5.0

3.9 IVUS measurements

IVUS measurements were obtained at the time of the procedure. As previously described, in cases allocated to the treatment group, these measurements were available to the surgeon to assist them in treatment decision-making. For cases allocated to the control group, the measurements were obtained in the same way as the treatment group but, due to the blinding process, were withheld from the surgeon.

IVUS measurements of the proximal and distal RVD were obtained at the most normal looking section, as defined by IVUS, adjacent to the lesion. The larger of the two RVD measurements was used as the IVUS RVD for the case. Ideally these measurements were obtained in sections of the vessel with less than 30% atheroma burden (defined as (EEM area-lumen area)/EEM area(25)), however if no sections of the vessel met this criterion then the most normal section available was used. These measurement points were defined purely on IVUS criteria and did not need to be at the same level in the vessel as those used for angiographic measurements. IVUS diameter and area measurements were obtained from axial images following consensus guidelines(231). The measurement software on the IVUS system was used to obtain diameter and area measurements. Each RVD was measured in mm and was the mean of two diameter measurements obtained in orthogonal planes. The area measurement was measured in mm^2. The measurement process was to activate the automated contour estimation function to obtain perimeter estimates of the lumen and the EEM. This was then adjusted manually as required to ensure accurate matching of the actual and measured circumferences (Figure 3.3). EEM area estimates were not recorded if there was greater than 45º of calcification obscuring the media/adventitia interface(252).

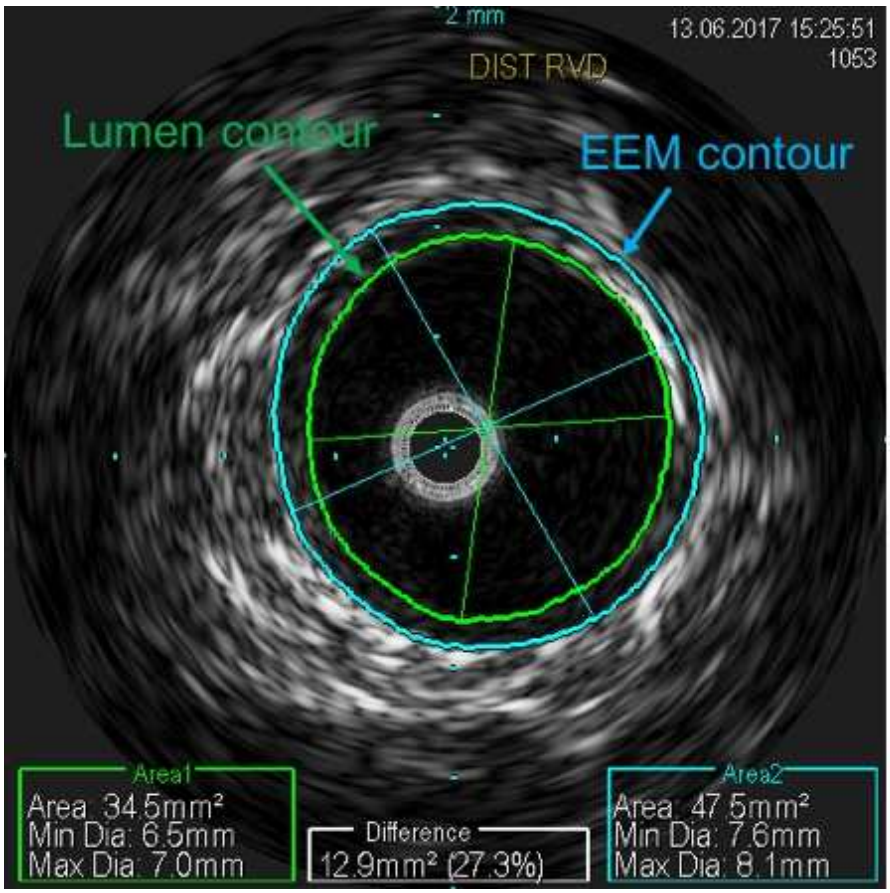

Figure 3.4 Cross-sectional IVUS image of normal artery with lumen and EEM contours adjusted to the lumen-intima boundary and media-adventitia boundaries respectively

Lesion length (mm) was measured using visual assessment of the IVUS imaging of the proximal and distal edge of the lesion to define the maximum extent of disease on the IVUS imaging. The positions on the radio-opaque ruler of the proximal and distal extent of the lesion were then located using the bookmarks, bony landmarks and branching vessels, and an estimation of lesion length obtained.

3.10 Data collection

The candidate performed all data collection. Data was collected from a variety of sources including directly from participants, from medical records, from the hospital and state-wide medical information systems, from the state-wide PACS system and from private imaging providers. Data was collected prior to the procedure, during the procedure and for a one-year period after the procedure. Private medical records were accessed for participants who had opted for private follow-up outside the state public health system with the consent of the participant and their treating surgeon.

3.10.1 Patient, vessel and lesion characteristics

Patient demographics, previous medical history, co-morbidities, risk factors and medication information were collected. Lesion characteristics from angiographic and IVUS imaging were obtained during the endovascular procedure from initial angiography and IVUS imaging recorded prior to commencement of the treatment. This included angiographic and IVUS measurements of the RVD and lesion length (mm), the type of lesion (de novo stenosis, de novo occlusion and restenosis), lesion location, the TASC II lesion classification(222), the degree of calcification in the lesion graded using the PACSS scoring system(17), and the number of patent tibial (runoff) arteries.

3.10.2 Procedural information

Procedural information including the type of access, the type of treatment method(s) used, the size of balloons and stents used, the number of stents used, the length of treatment, treatment to non-femoropopliteal arteries in the same limb during the same procedure, the final result on completion imaging and any complications encountered during the procedure was obtained.

The following information related specifically to the RCT was recorded: the randomisation status, whether IVUS was performed, whether post treatment IVUS was obtained, disagreement between the angiographic and IVUS findings (both pre and post-treatment) and the nature of the disagreement, the treatment plan based on the angiographic imaging, the treatment plan based on the IVUS imaging (only applicable for cases in the treatment group), whether there was a change in the treatment plan due to the IVUS findings and the nature of the treatment change (only applicable to the treatment group).

Types of disagreement between angiographic and IVUS in pre-treatment included:

- Difference of ≥0.5mm in pre-treatment RVD
- Difference of ≥20mm lesion length estimation
- Difference in severity of stenosis estimation (a significant difference was considered to be one that changed the lesion from not requiring treatment to requiring treatment, using a threshold of ≥50% stenosis)
- Difference in assessment of plaque eccentricity sufficient to rule out the use of directional atherectomy (defined as highly eccentric plaque with areas of exposed normal wall)
- In cases being treated for ISR, a difference in pre-treatment stent appearances that might change the treatment plan (e.g. appearances that might preclude the use of atherectomy, such as lumen narrowing due to inadequate stent expansion rather than NIH or highly eccentric NIH that might preclude atherectomy).

Post treatment disagreements between angiographic and IVUS in post-treatment included:

- Difference in the severity categorisation for residual stenosis or dissection (with the threshold for differentiating mild and severe dissection/residual stenosis defined as ≥30% lumen diameter reduction compared to the RVD)
- Difference in adequacy of stent expansion (defined as a narrowing of the stent on subjective assessment of angiography or by a MSA <15.5mm^2 on IVUS (68))
- Difference in assessment of stent apposition (with malappositon defined as evidence of at least one free floating stent strut).

3.10.3 Clinical follow-up

Participants were routinely followed up as outpatients at six weeks, three months, six months and twelve months. Due to the nature of the study, treating surgeons were aware of the randomisation in the clinical follow-up period however they remained blinded to the IVUS results for participants in the control group. The hospital and state-wide information system was accessed to check whether participants had presented to the hospital, or to other sites, for imaging, pathology testing or treatment of any kind. Re-intervention on the treated artery (both endovascular and surgical), episodes of care for vascular complications, and major adverse events (MAE) were recorded. The hospital epidemiology service obtained all state-wide admissions after the index procedure for participants in the study and identified all the International Statistical Classification of Disease and Related Health Problems (ICD-10) codes associated with these admissions. This data was then searched for codes related to major adverse events and these were entered into the study database.

3.10.4 Surveillance testing

Surveillance duplex ultrasonography was scheduled for three, six and 12 months (+/- one month) after the procedure in all participants. Duplex ultrasound scans were performed by a variety of imaging providers due to the geographical dispersal of the participants. Imaging providers were provided with normal clinical history information to enable performance of the surveillance scan but were blinded to the randomisation of study participants.

Participants in the metropolitan area were scanned by either the hospital outpatient imaging service or a private provider contracted to provide ultrasound imaging services. Local imaging providers scanned participants from regional and remote locations outside the metropolitan area. Scans were performed a variety of ultrasound systems all of which had vascular specific transducers and imaging software modules available.

All scans were performed following a standardised imaging protocol including B-mode, colour

Doppler and pulsed wave (PW) Doppler assessment of the infra-inguinal arteries of the treated side, including the CFA, SFA, popliteal and all tibial arteries. Imaging was performed using linear array transducers with a centre frequency of 7MHz using vascular specific pre-set function to ensure that key B-mode and Doppler parameters such as pulse repetition frequency, dynamic range, gain, sweep speed and wall filter were optimised and standardised for arterial imaging. All PW Doppler sampling was performed with a Doppler angle between 30 and 60°. Peak velocity measurements (in cm/sec) were obtained and recorded for each segment of the infra-inguinal arteries. B-mode and colour Doppler was used to assess for evidence of stenosis and additional PW Doppler sampling was obtained proximal, within and distal to any areas of suspicion for stenosis. The peak velocity ratio (PVR) was defined according the following equation:

$$\text{PVR} = \frac{\text{max peak velocity at stenosis}}{\text{peak velocity in normal segment immediately proximal to lesion}}$$

and binary restenosis (≥50% stenosis) was defined as a PVR ≥ 2.4(253-255).

All scans were available for review by the medical staff at the treating hospital as part of standard care. It was recognised that the operator dependent nature of ultrasound and the use of multiple sonographers introduced a potential source of bias into the surveillance process. All scans were therefore reviewed by the candidate to assess for technical compliance. This involved assessing the ultrasound images to confirm that all segments of the treated artery had been imaged and an assessment of the technical parameters that might influence accuracy of the duplex findings. These included that an appropriate angle of insonation was used to ensure that velocity measurements were reliable (defined as an angle between 45-60° to the direction of flow), that an appropriate pulse repetition frequency was used to ensure accurate display of PW Doppler waveforms, that the sample volume was positioned in the centre of the artery to ensure that the maximum velocity was displayed and that caliper placement was appropriate for measurement of the peak systolic velocity. All scans met the required standard and and there were no cases where repeat scanning was necessary.

3.10.5 Outcome Measures

The primary outcome measure for this trial was binary restenosis within 12 months. Binary restenosis was defined as ≥50% stenosis within 12 months post procedure on duplex ultrasound. Outcomes were described in terms of freedom from binary restenosis and this was defined as the absence of binary restenosis on imaging during the follow-up period. Binary restenosis was the preferred over the term “patency” as it more clearly and precisely described the parameter(256). Surveillance imaging was performed by duplex ultrasound. CTA or angiographic imaging was not used for routine scheduled surveillance but results from these forms of imaging were collected if

they were performed for clinical reasons within the study follow-up period. For these modalities restenosis was defined as ≥50% stenosis using the methods described by Diehm et al (256). As this was a time-based analysis, the median time of the 12-month follow-up duplex scan for each group was calculated and tested for a difference in the timing of this scan between the two groups. This was assessed due to the potential of differences in the time to 12-month follow-up to affect the results for binary restenosis. For example, if the time to final follow-up was significantly shorter in one group compared to the other this might decrease the apparent binary restenosis rate in that group due to subjects having less time for restenosis to develop.

TLR was defined as a repeat procedure (endovascular or surgical) to treat the originally treated lesion. This included treatment 1 cm proximal or distal to the lesion to account for edge related restenosis(257). Freedom from TLR was defined as the absence of TLR during the follow-up period of 12 months.

A combined outcome of binary restenosis or death was also recorded to allow investigation of whether the censoring of participants due to death had an effect on the survival analysis results for binary restenosis.

Major adverse events (MAE) were recorded for the 12 months following the procedure. MAE represents a combined measure of major adverse limb events (MALE) and major adverse cardiovascular events (MACE) as described by Diehm et al.(256). MACE and MALE were also analysed as separate categories to enable assessment of each of these events for the control and treatment groups. Events included in MACE were death, myocardial infarction and stroke. Events included in MALE were acute (defined as within 30 days of the index procedure) re-intervention for a limb-related complication (defined as surgical or endovascular treatment of perforation, false aneurysm, thrombosis or thromboembolisation, including thrombolysis) and major amputation (defined as amputation proximal to the ankle). Cases of re-intervention for restenosis or occlusion of the target lesion (TLR) during the follow-up period were not reported as MAE cases as they were reported as a separate category. These events were recorded to enable assessment of any differences in these events between the treatment and control groups. This was performed in case there were differences between the groups for events that might be related to failure of the treatment procedure, such as major amputation or re-intervention for procedure-related complications, and for events that may not be related to the treatment procedure such as cardiovascular events. Cardiovascular events were included as these might indicate an over-all deterioration in patient condition but also because they might have some other influence on patient management over the follow-up period, for example by providing an opportunity, outside normal clinical follow-up, for optimisation of medical therapy or for the performance of non-scheduled imaging that may change patient management.

Peri-procedural complications were defined as thromboembolism, perforation, false aneurysm, cardiovascular event or other systemic event during or immediately after the procedure. This included minor complications, defined as being successfully treated during the procedure, and major complications, defined as requiring further intervention or other treatment after the procedure.

The 30-day complication rate was also recorded as a separate outcome and included any of the following in the first 30 days: major procedural complications, major amputation, major adverse cardiovascular events, unplanned extension of hospitalisation and hospital re-admission.

Procedural success was defined as technical success (<30% residual diameter stenosis and no flow-limiting dissection) without a major adverse event or re-intervention for a procedure related complication during the hospital stay(256).

3.11 Statistical analysis

Survival analysis using Kaplan-Meier curves for the control and treatment groups was assessed for the primary outcome measure of time to binary restenosis within 12 months post index procedure. For the purposes of this analysis, survival was considered to be freedom from the specified end point, e.g. binary restenosis. The difference in survival was tested for statistical significance using the Log-rank test, with the null hypothesis being no difference between the survival curves for the control and treatment groups. Analysis was based on the intention-to-treat principle with all participants who received treatment remaining in the analysis(258, 259). Participants who had died or who did not receive 12-month follow-up surveillance duplex scans were censored for survival analysis of binary restenosis at the date of their last follow-up duplex scan. The “last observation carried forward” method was not used due to considerable risks of introducing bias and lack of evidence supporting this practice(260).

For TLR and MAE, participants were censored at the date of death, date of withdrawal from the study or loss to follow-up. Survival analysis was also performed using Kaplan-Meier curves for freedom from TLR and freedom from a MAE within 12-months post index procedure. As with binary restenosis, all participants remained in the analysis.

For the combined outcome of binary restenosis or death, survival analysis was performed with the time to event being the time to last normal surveillance duplex scan for those with restenosis and alive at 12 months and the time to death for those free of binary restenosis at the time of death.

Statistical significance for survival analysis was set at p=0.01 for interim analysis when 70% of subjects had achieved one-year follow-up and p=0.04 at completion of one year follow-up for all subjects in the target sample(238).

Continuous data was reported as mean (SD) or median (IQR) depending on whether the distribution approximated normality. Categorical data was presented as n (%). Testing for difference between groups for continuous data was performed using independent sample t-test or the Mann-Whitney U test depending on whether the distribution approximated normality. Testing of difference between groups for categorical data was performed using the chi-square test or Fisher's exact test for dichotomous variables when a result of ≤5 was expected.

Agreement between angiography and IVUS measurements methods was assessed by testing of differences and by the use of Bland-Altman plots, with limits of agreement analysis (261) performed if data approximated normality(261, 262). Assessment of relationships between variables was performed using Pearson's or Spearman's correlation coefficient depending on whether the distribution approximated normality. Logistic regression analysis was used to ascertain the effects of study variables on clinical outcome measures.

All statistical analysis was performed using SPSS Statistics for Windows version 24 (IBM Corp, Armonk, NY). The significance level of all testing was set at a p-value <0.05, except for reporting of interim outcomes as noted above.

4 THE IMPACT OF INTRAVASCULAR ULTRASOUND ON OUTCOMES OF ENDOVASCULAR TREATMENT OF FEMOROPOPLITEAL DISEASE: RESULTS

4.1 Introduction and aims

IVUS technology is widely used in percutaneous coronary interventions however its use in peripheral endovascular interventions has been much more limited. From the review of the IVUS literature detailed in the previous chapter it is clear that there is convincing evidence that IVUS imaging is more accurate than angiography for delineating vessel and disease characteristics (11, 13, 51, 74, 80). While there is an extensive body of literature that has used IVUS to study the effects of a variety of therapies in the peripheral arteries, there is limited evidence in regards to whether the use of IVUS during endovascular treatment in the peripheral arteries improves outcomes. The studies addressing this question in the peripheral arteries are all retrospective and, as discussed in chapter 2, provide limited guidance for clinical practice due to the specific nature of the treatments investigated(143, 175), the lack of procedural information (14, 15) and limited outcome measures reported(15). There are no prospective studies investigating the impact of IVUS imaging information on clinical decision-making and on clinical outcomes. The lack of clear evidence for the use of IVUS is reflected in a reported rate of usage of IVUS of less than 2% of cases in lower limb interventions(16). It is also currently unclear what impact the use of IVUS has on the choice of treatment of peripheral artery lesions. There is evidence from the coronary literature that the use of IVUS can result in a change in the treatment in 48-74% of cases (5, 105, 152) but there is no equivalent data available for peripheral interventions.

4.1.1 Study aims

The aims of this study were to investigate whether femoropopliteal artery interventions using combined IVUS and angiographic imaging result in a lower rate of binary restenosis within 12 months for participants with severe claudication or CLI compared to interventions utilising angiography only, and to quantify how often and in what ways IVUS changes the endovascular treatment performed.

4.1.2 Research questions

This chapter will present and discuss the findings from research performed to answer the following research question related to the aims stated in section 4.1.1.

Research question 1 (RQ1): Will the addition of IVUS imaging to femoropopliteal artery endovascular interventions result in a reduction in binary restenosis within 12 months in

participants being treated for severe claudication and CLI.

4.1.3 Hypothesis

The hypotheses related to the aims and research questions were:

Hypothesis 1: That interventional procedures using combined IVUS and angiographic imaging will have a lower rate of binary restenosis within 12 months compared to interventions using angiography alone.

4.2 Results

4.2.1 Patient demographics and lesion characteristics

At the time of writing, one-year follow-up for the primary outcome measure of binary restenosis was available for 107 participants recruited for the study (53 allocated to the control group and 54 allocated to the treatment group). Recruitment and retention into the study is outlined in the CONSORT flow diagram (Figure 4.1). There was no significant difference in the number of participants in each group who did not undergo surveillance duplex ultrasound assessment at one year (11 participants in the control group and nine participants in the treatment group, p=0.766 chi-square test). Of these participants, three died prior to one year in the control group and two died in the treatment group. There were a variety of reasons why the other participants did not have a surveillance duplex scan at one year and these are outlined in Figure 4.1. All other participants either had the one year surveillance duplex ultrasound scan performed or had already been found to have binary restenosis on an earlier scan.

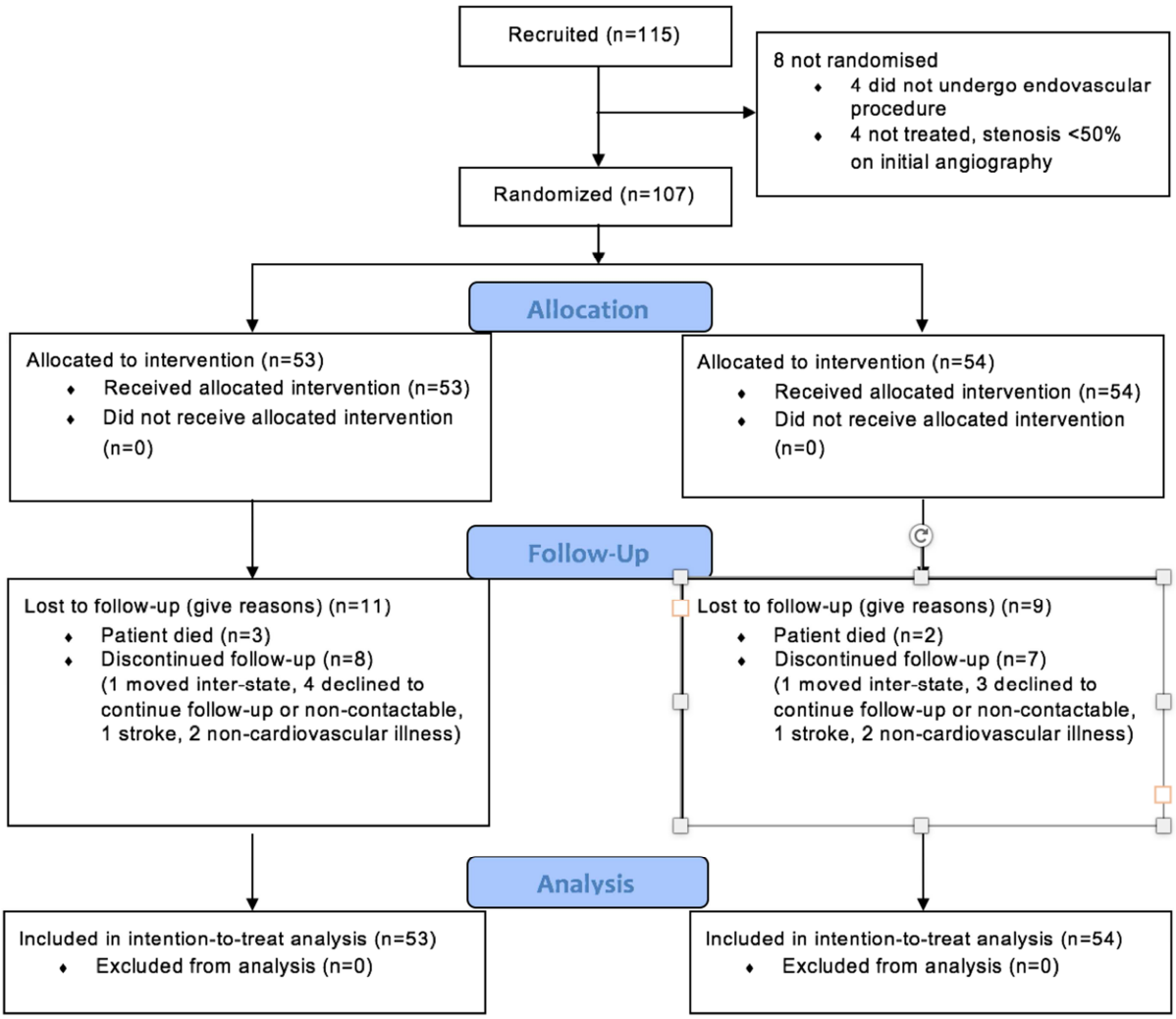

Figure 4.1 CONSORT RCT flow diagram

Patient characteristics for each group are presented in Table 4.1. There no significant differences for any parameters between the two groups. When considered as a single group; the participants had demographics, co-morbidities and risk factors expected for people presenting with peripheral arterial disease. Participants were elderly (mean age 74.0 years) and primarily male (66 of 107). Risk factors, in order of prevalence, were hypertension (83.2%, 89 of 117), history of smoking (79.4%, 85 of 107), hyperlipidaemia (75.7%, 81 of 107), renal insufficiency (54.2%, 58 of 107), ischaemic heart disease (50.5%, 54 of 107) and diabetes (42.1%, 45 of 107) of cases. Participants presented with claudication in 61.70% (65 of 107) of cases and CLI in the remaining 39.3% (42 of 107). A previous history of peripheral artery intervention (48.6%, 52 of 107) was more common than coronary artery intervention (34.6%, 37 of 107), while a previous history of stroke/TIA (5.6%, 6 of 107) or major lower limb amputation (2.8%, 3 of 107)) were far less common. The majority of participants were receiving aspirin (83.2%, 89 of 107) and statins (69.2%, 74 of 107) at the time of treatment, but fewer had been prescribed angiotensin converting enzyme inhibitors (ACEi) (38.3%, 41 of 107) or clopidigrel (32.7%, 35 of 107).

Table 4.1 IVUS RCT patient characteristics for the control and treatment groups

	Control group (angiography) (n=53)	Treatment Group (IVUS and angiography) (n=54)	p value
Mean age, years (SD)	74.2 (9.9)	73.2 (10.0)	0.609*
Gender (male)	30	36	0.284†
Mean BMI (kg/m^2) (SD)	28.5 (5.1)	28.8 (4.3)	0.673*
Smoking history			
Never	10	12	
Ex-smoker	31	34	
Current	12	8	0.574†
Diabetes mellitus	21	24	0.613†
IHD	29	25	0.384†
HT	43	46	0.575†
Hyperlipidaemia	38	43	0.374†
GFR (ml/min)	56.8 (25.8)	59.0 (23.4)	0.644*
Renal insufficiency (<60ml/min) (SD)	27	31	0.502†
Rutherford 3	31	34	
Rutherford 4-5	22	20	0.636†
Previous coronary artery bypass or PCI	16	21	0.344†
Previous peripheral arterial intervention	28	24	0.386†
Stroke/TIA	5	1	0.113‡
Major amputation	3	0	0.118‡
Aspirin	43	46	0.575†
Clopidigrel	16	19	0.582†
Statin	37	37	0.885†
ACEi	20	21	0.902

* Independent sample t-test, †Pearson chi-square, ‡Fisher's exact test

4.2.2 Lesion and vessel characteristics

Vessel and lesion characteristics are presented in Table 4.2. There was a non-significant difference in lesion length (the median lesion length in the control group was 20mm longer), but no significant difference in any parameters between the two groups.

When lesion characteristics for the entire sample are considered, it was found that just under half of lesions were located in the SFA (48.6%, 52 of 107), 22.4 (24 of 107) were in the popliteal artery and 29.0% (31 of 107) involved both the SFA and popliteal; arteries. Just over half of lesions were stenotic (≥50% diameter stenosis) (56.1%, 60 of 107), 30.8% were chronically occluded (occluded for at least three months) (33 of 107) and 13.1% (14 of 107) were re-stenotic after previous treatment. There were two or three run-off vessels present in 68.2% (73 of 107) of cases. Severe vessel calcification was present in 41.1% (44 of 107) of cases (PACSS grades 3 and 4).

Table 4.2 Vessel and lesion characteristics for the control and treatment groups

	Control group (angiography) (n=53)	Treatment Group (IVUS and angiography) (n=54)	p value
Lesion location			
SFA	26	26	
SFA/popliteal artery	10	14	
Popliteal artery	17	14	0.623*
Median angiographic lesion length, mm (IQR)	120 (145)	100 (114)	0.094‡
Mean angiographic RVD, mm (SD)	5.07 (0.88)	5.15 (0.87)	0.651†
Lesion type			
Stenosis	29	31	
CTO	16	17	
Restenosis	8	6	0.830*
Runoff vessels			
0	**1**	**0**	
1	19	14	
2	18	22	
3	15	18	0.490*
PACSS calcification score			
0	15	21	
1	12	12	
2	0	3	
3	2	3	
4	24	15	0.180*

* Pearson chi-square, † Independent sample t-test, ‡Mann-Whitney U test

4.2.3 Procedural information

Procedural information is presented in Table 4.3.

Table 4.3 Procedural information for control and treatment groups

	Control group (angiography) (n=53)	Treatment Group (IVUS and angiography) (n=54)	p value
Access			
Contralateral	28	27	
Ipsilateral	25	27	0.770*
Mean device size, mm (SD)	5.65 (0.73)	5.85 (0.68)	0.145†
Median treatment length, mm (IQR)	140 (190)	130(100)	0.983‡
Treatment type			
POBA	4	4	
DCB	31	35	
BMS	6	7	
DCB and BMS	5	5	
CS	5	0	
DES	2	3	0.357*
Treatment (dichotomised)			
POBA/DCB	35	39	
Stent	18	15	0.489*
Secondary stenting	11	10	0.771*
Adjunctive atherectomy	9	11	0.653*
Median length of stented segment, mm (IQR)	110 (73)	80 (60)	0.093‡
Stent number			
0	36	39	
1	12	11	
2	3	4	
3	2	0	0.513*
Additional interventions			
None	41	38	
Iliac arteries	1	2	
CFA	1	2	
Tibial arteries	9	11	
More than one artery	1	1	0.914*

*Pearson chi-square, †Independent t-test, ‡Mann-Whitney U test

The length treated with a stent was less in the treatment group compared to the control group although this did not reach statistical significance. There was no difference in any other parameters. Just under two thirds of cases (69.2%, 74 of 104) were treated with angioplasty (either POBA alone of POBA/DCB) with the rest having some form of stenting. Atherectomy was performed in 18.7% of cases (20 of 107).

4.2.4 Comparison of IVUS and angiographic imaging

In three allocated to the control group, IVUS measurements could not be obtained. In two cases

this was during the period that the IVUS machine was shared and it was urgently required by other users after randomisation had occurred and in one case this was due to failure of the catheter during initial imaging with a replacement catheter being unavailable. These patients were retained in the trial for assessment of outcomes as the lack of IVUS imaging did not affect the treatment and therefore their retention in the control group would not affect the results of the primary outcome. The comparison of imaging findings between the imaging modalities was therefore restricted to the 104 cases obtained with both angiography and IVUS images available.

4.2.4.1 Comparison of angiographic and IVUS measurements of reference vessel diameter and lesion length

The mean RVD and lesion length for angiography and IVUS are presented in Table 4.4. IVUS measurements were significantly larger for both RVD and for lesion length.

Table 4.4 Mean RVD and lesion length as measured by angiography and IVUS (n=104)

	Angiography	IVUS	P value
Mean RVD, mm (SD)	5.13 (0.87)	5.59 (0.92)	<0.001*
Median lesion length, mm (IQR)	100 (140)	120 (160)	0.030†

* Independent samples t-test, †Mann-Whitney U test

A Bland-Altman plot of IVUS and angiography measurements of RVD showed a wide range in the difference between angiography and IVUS (Figure 4.2). Limits of agreement analysis found a systematic bias toward a larger RVD with IVUS assessment (mean of the differences=0.46mm, 95% CI: -0.33mm and 1.24mm).

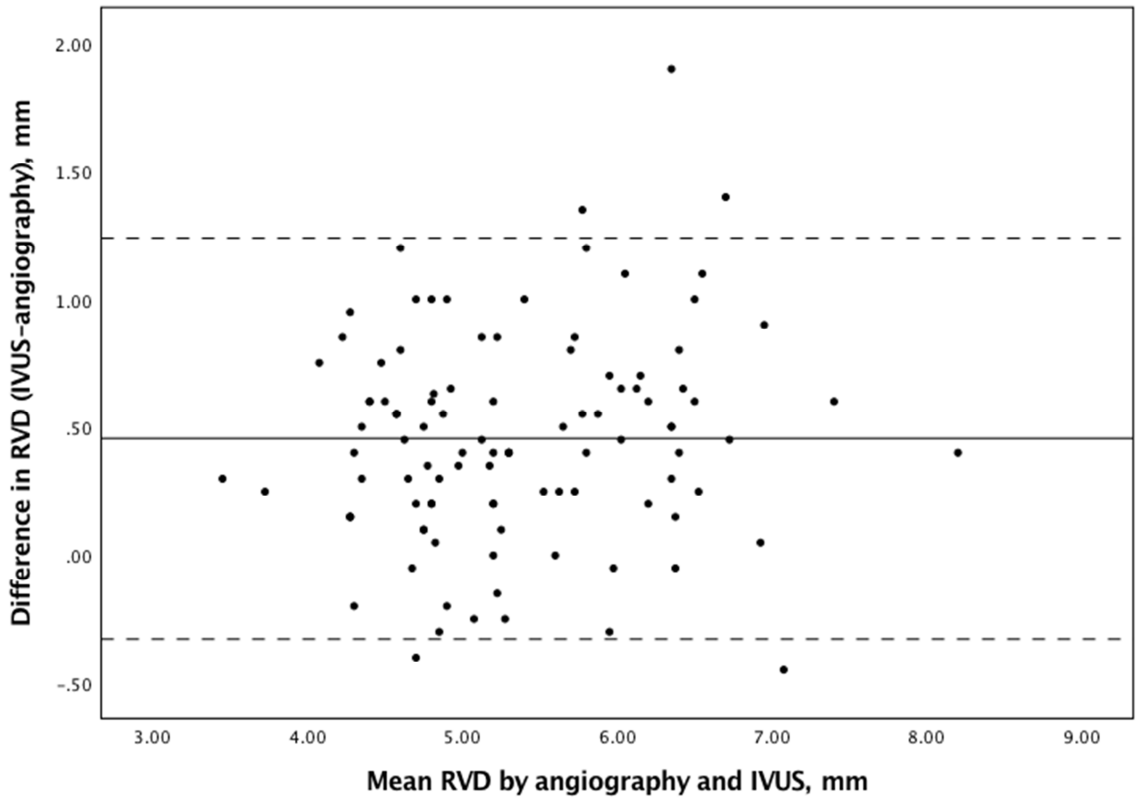

Figure 4.2 Bland Altman plot with limits of agreement for IVUS and angiographic RVD measurements. Solid line represents the mean difference between the IVUS and angiographic measurements, the dotted lines represent the 95% limits of confidence

A Bland Altman plot of lesion length measurement by IVUS and angiography (Figure 4.3) showed that the IVUS measurement was larger in almost all the cases where there was a difference between the measurements. This suggests that there was a likely to be a systematic bias toward a longer lesion length. The plot shows that there was a wide dispersal toward larger IVUS length measurements with just under 10% of cases having a difference between IVUS and angiography ≥100mm. Limits of agreement plot testing was not performed for lesion length due to the lack of approximation to normality of the distribution.

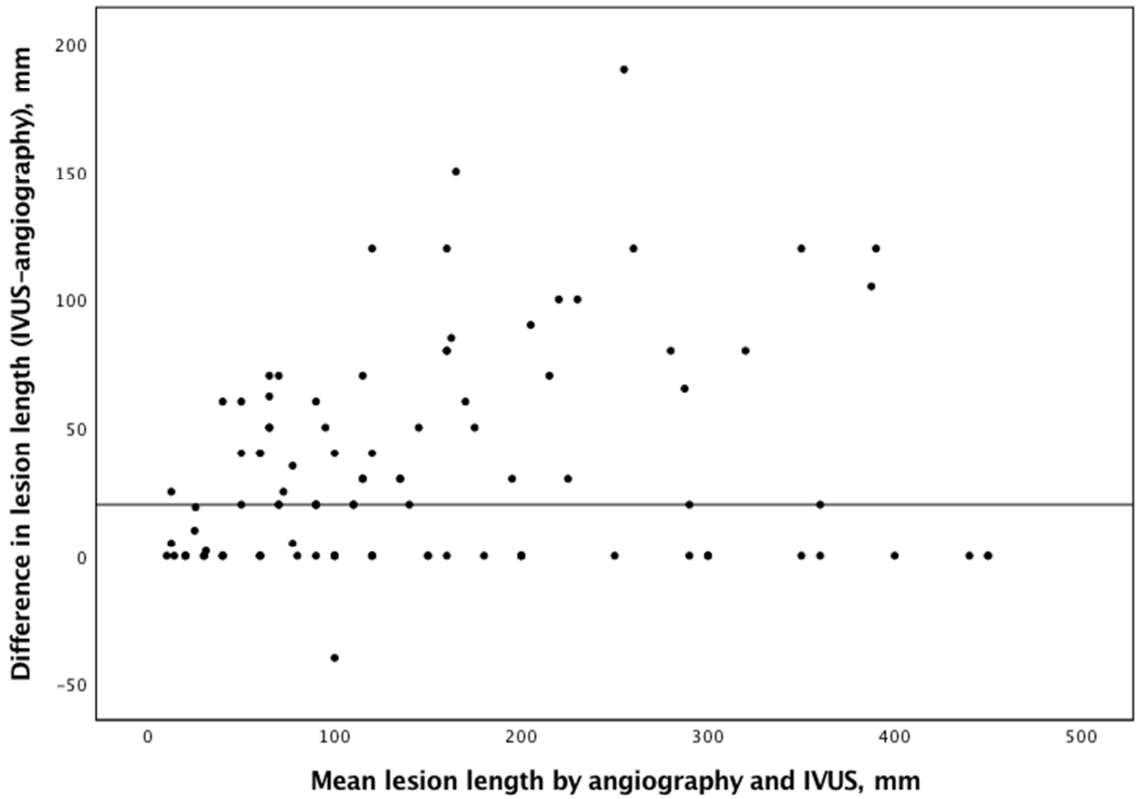

Figure 4.3 Bland Altman plot of IVUS and angiographic lesion length measurements. Solid line represents the median difference between the IVUS and angiographic measurements

4.2.4.2 Relationship between angiographic measurements and device size or treatment length over the duration of the study

There was a small negative correlation between the chronological order of performance of procedures and the difference between device size and angiographic diameter (Pearson r=-0.162, p=0.248). There was no correlation between the chronological order of performance of procedures and the difference between the length treated and the angiographic lesion length (Spearman rho=0.106, p=0.450).

4.2.4.3 Disagreement in imaging findings

There was disagreement in imaging findings between the IVUS and angiography in 79.8% (83 of 104) cases (Table 4.5). The total number of occurrences of different types of disagreement was also larger in the treatment group compared to the control group. In total, there were 110 different types of disagreement in findings, with one type of disagreement present in 83 cases, two types of disagreement in 26 cases and three types of disagreement in one case. Differences related to lesion length accounted for 46.4% of episodes of disagreement, (51 of 110), 37.2% were related to vessel diameter (41 of 110), 13.6% (15 of 110) were related to post-treatment appearances and in two cases were related to plaque appearances.

Table 4.5 Differences in imaging findings between IVUS and angiography for each group

	Control group (angiography) (n=53)	Treatment Group (IVUS and angiography) (n=54)	p value
Cases with disagreement between in findings	39 (78.0%)	44 (81.5%)	0.844
Occurrences of different types of disagreement	50	60	
RVD	21	20	
Lesion length	21	31	
Post-treatment appearances	7	8	
Plaque appearances	1	1	

*Chi-square test

4.2.5 Binary Restenosis

There was a significantly higher percentage of participants in the treatment group who were free from binary restenosis within one year compared to participants in the control group (treatment=77.8%, control=56.6%, Log-rank p=0.007) (Figure 4.4).

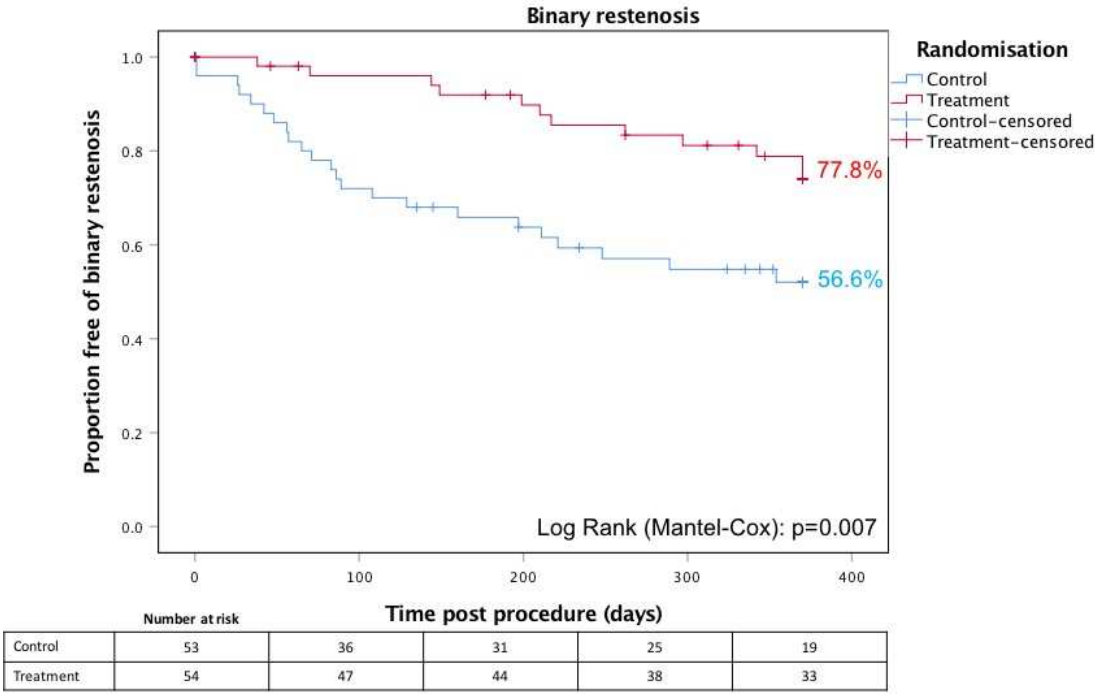

Figure 4.4 Kaplan-Meier graph of binary restenosis within one year for the control and treatment groups

The mean time period to the 12-month surveillance scan was 372 days for the control group and 376 days for the treatment group (p=0.411, independent samples t-test).

4.2.6 Other outcomes

There was no significant difference in freedom from TLR within one year between the two groups (treatment=92.6% vs. control=84.9%, Log-rank p=0.195) (Figure 4.5).

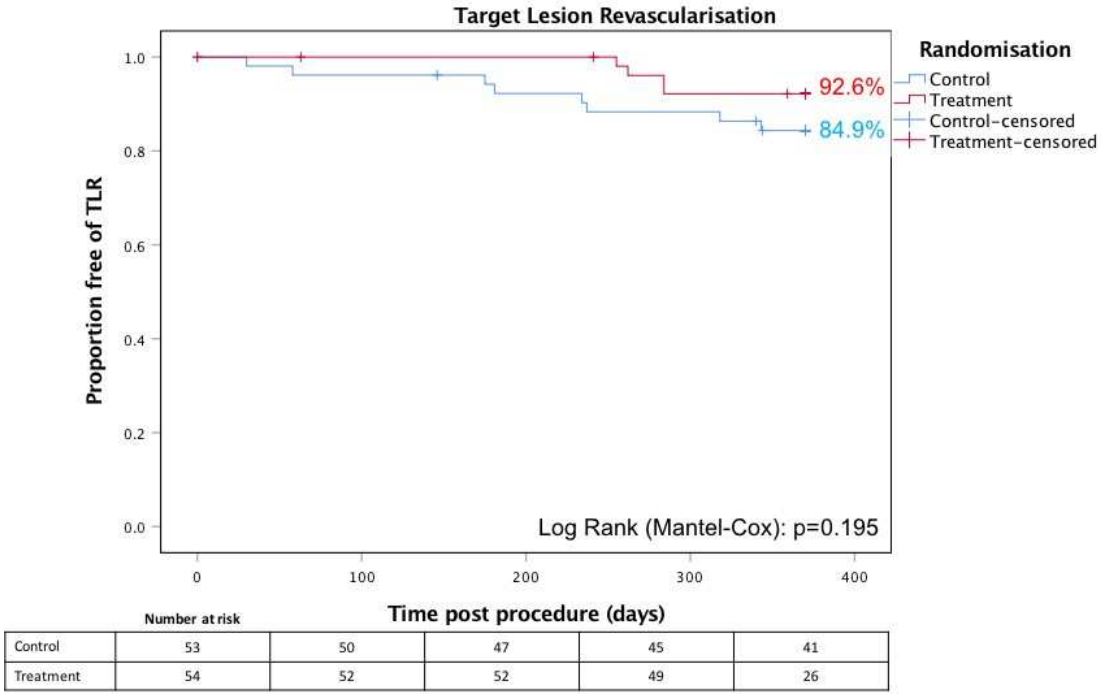

Figure 4.5 Kaplan-Meier graph of TLR within one year for the control and treatment groups

MAE occurred in 22 participants within one year of treatment. There were 23 separate MAE events, with one participant having two events within the one-year period. The types of events for each group are presented Table 4.6. There was no significant difference in freedom from MAE between the two groups (treatment=81.5% vs. control=77.4%, Log-rank p=0.598) (Figure 4.6).

Table 4.6 Types of MAE that within one year of the post index procedure

	Control group (angiography) (n=53)	Treatment Group (IVUS and angiography) (n=54)	Significance*
Death	3	2	0.679
TIA/Stroke	3	6	0.489
MI	2	1	0.618
Major amputation	1	1	1.000
Procedure related re-intervention	1	0	0.495
Thrombolysis	0	1	1.000
Re-admission	2	0	0.243

*Fisher's exact test

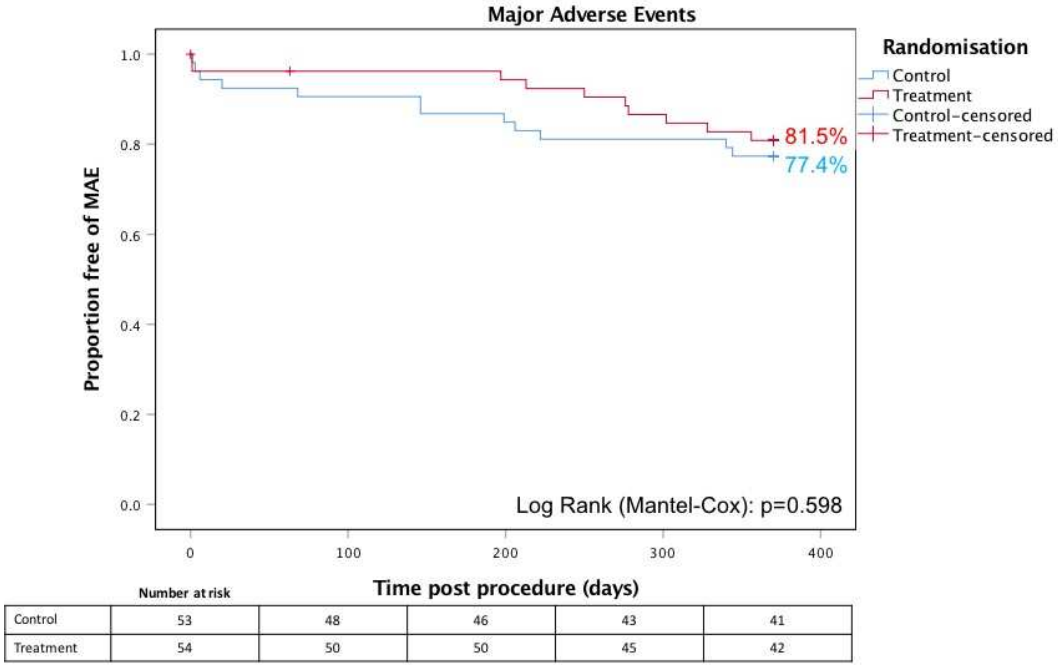

Figure 4.6 Kaplan-Meier graph of MAE within one year for the control and treatment groups

MACE occurred within one year in eight participants in the control group and in eight participants in the treatment group (p=0.832, Log Rank test). MALE occurred within one year in four participants in the control group and in two participants in the treatment group (p=0.402, Log Rank test).There was a significantly higher percentage of participants in the treatment group who were free from binary restenosis or death within one year compared to participants in the control group (treatment=75.9%, control=52.8%, Log-rank p=0.004).

There were five cases with peri-procedural complications (4.7% of cases), with two in the control group and three in the treatment group (3.8% and 5.6% respectively, p=1.000, Fisher's exact test). Three of the five peri-procedural complications were successfully treated during the procedure. There were no cases with residual stenosis >30% or flow-limiting dissection at the end of the procedure. There were two cases with complications that required further treatment during the same admission (one case of thromboembolism requiring overnight thrombolysis and one case of re-intervention to repair an arterial perforation) and these therefore represent the total number of cases of procedural failure. The procedural success was rate was therefore 98.1% (105 of 107 cases). There was no significance difference in procedural success rate between the control (98.1%, 49 of 53) and treatment (98.1%. 51 of 53) groups (p=1.000, Fisher's exact test).

There were seven complications in the 30-day period after the procedure (6.5% of cases), with five complications in the control group and two in the treatment group (9.4% vs. 3.7% respectively, p=0.211, Fisher's exact test).

4.2.7 Treatment changes in the treatment group (IVUS and angiography available)

The treatment plan was changed in 78.8% (42 of 54) of cases in the treatment group. There were 49 specific changes to the treatment plan due to the IVUS findings, with one type of treatment change in 36 cases, two types of change in five cases and three types of change in one case. Increases in the treatment length or size of the treatment device were the most common types of change, constituting 83.7% of the episodes where there was a change in treatment (Table 4.7).

Table 4.7 Types of change in the treatment plan due to IVUS findings

Treatment change	n=49	% of total number of cases with a change to the treatment plan (n=42)
Increase in treatment device size	16	38.1%
Increase in treatment length	25	59.5%
Change after initial treatment completed	5	11.9%
Change in treatment modality	3	7.1%

Note: the total of % for each type of treatment is greater than 100% due to there being more than one change in six cases.

Cases that had a changes after initial treatment included the following: three cases of post-angioplasty dissection that were categorised as mild on angiography but were re-ballooned due to ≥30% lumen diameter decrease seen on IVUS; one case of residual stenosis categorised as mild on angiography that subsequently underwent secondary stenting due to ≥30% lumen diameter decrease on IVUS; and one case with adequate stent deployment on angiography that underwent repeat angioplasty due to inadequate lumen on IVUS (MSA <15.5mm^2). The change to the treatment modality included two cases in which the original plan was modified from using primary adjunctive atherectomy to using angioplasty without prior atherectomy due to highly eccentric nature of the plaque seen on IVUS, and one case with a second lesion that had a mild stenosis on angiography that was treated with angioplasty due to IVUS demonstrating a >50% stenosis.

4.2.8 Predictors of binary restenosis

A logistic regression was performed to ascertain the effects of RVD, the presence of severe calcification and the use of DCB on the likelihood that participants have binary restenosis within one year of the index procedure (Table 4.8). The logistic regression model was not statistically significant, $\chi^2(3) = 7.58$, $p = 0.056$. The model explained 9.5% (Nagelkerke R^2) of the variance in binary restenosis and correctly classified 67.3% of cases. RVD and severe calcification were not significant predictors of restenosis. The use of DCB was a significant negative predictor for restenosis. The power of this analysis is likely to be reduced due to the small sample size available.

Table 4.8 Logistic regression analysis of predictors of binary restenosis

	O.R.	95% C.I. for O.R.		
		Lower	Upper	Sig.
RVD by angiography (mm)	1.13	0.67	1.90	0.651
Severe calcium (PACSS 3&4)	1.91	0.78	4.67	0.157
DCB treatment	0.38	0.16	0.88	.023

.When only cases treated with DCB were considered, there were significantly fewer cases of binary restenosis in the treatment group compared to the control group (Table 4.9).

Table 4.9 2x2 contingency table of binary restenosis in treatment and control groups for cases treated with DCB

	No binary restenosis	Binary restenosis	Total
Treatment group	32	3	31
Control group	18	13	33
Total	50	16	66

p=0.003, Fisher's exact test

4.3 Discussion

4.3.1 The effect of IVUS imaging on one-year outcomes

These results are an interim analysis of the first prospective randomised trial of the use of IVUS in peripheral endovascular interventions. The primary finding was that there were fewer cases of binary restenosis when the surgeon had access to both IVUS and angiography imaging compared to when angiography alone was available. This is the first prospective evidence that the use of IVUS in peripheral arterial interventions may improve outcomes and confirms the findings from retrospective studies of IVUS that have suggested a benefit from the use of IVUS(14, 15, 143, 175).

There was no significant difference in target lesion revascularisation rate between the control and treatment arms at this stage. The reasons for this are unclear although the TLR rate is typically lower than that for binary restenosis. The practice in this unit is for re-intervention to be driven by clinical need, in cases treated with angioplasty, rather than anatomical findings alone. The finding of restenosis therefore may not directly lead to re-intervention if there has not been a return of symptoms and a delay between the diagnosis of binary restenosis and re-intervention is not unexpected. Practice is more heterogeneous between surgeons in regard to cases of ISR. In these situations, there may be a lower threshold for re-intervention due to concerns regarding the risk of rapid progression of ISR to occlusion and the increased difficulty of treatment associated with stent occlusion. Less than a third of cases in this study were treated with stents in this study and this may also be a contributor to the low TLR rate.

Comparison of the binary restenosis rate from the current study with recent trials is difficult because of the heterogeneity of treatments in the current study in comparison to available data from device specific trials. The type of device trials that would most closely match the current study are those that investigate the use of DCB as this was by far the most common type of treatment in the current study, accounting for roughly two thirds of all treatments. The freedom from binary restenosis rate in the control group for this study (55%) is lower than reported in recent device trials which report a range of 65%-82% for restenosis or primary patency (2-4). Care must be taken, however, when comparing results from different trials as these can be heavily influenced by study design, in particular the nature of the inclusion and exclusion criteria. The LEVANT1 and 2 trials (2, 4) excluded those with heavily calcified vessels, lesions longer than 15 cm, Rutherford 4 and 5 presentations, treatments involving adjunctive techniques such atherectomy and treatment in the P2/3 segments of the popliteal artery. The IN.PACT trial (3) excluded stenotic lesions >14 cm, occlusions >10cm and Rutherford 4 and 5 presentations. The lower rate of freedom from binary restenosis found in the control group of the current study may well relate to less restrictive inclusion and exclusion criteria, allowing the inclusion of patients who were more likely to be have poorer outcomes. These included lesion length (median lesion length in the current study of

120mm compared to mean lengths of 80.5mm in LEVANT 1 and 68mm in IN.PACT), inclusion of Rutherford 5 presentations, inclusion of occlusions >10cm and severe calcification (41% severe calcification in the control group compared 8% calcification in IN.PACT and exclusion of severe calcification in LEVANT 2).

The outcome measure results presented in this report are still preliminary as the results are from a subgroup of participants who had reached one-year follow-up since the index procedure at the time of writing. There were 43 participants still to reach one-year follow-up and more conclusive results will not be available until follow-up is available for the entire target sample.

4.3.2 Comparison of IVUS and angiography imaging findings

There was trend toward a larger measurement of the RVD with IVUS compared to angiography. The mean RVD obtained with IVUS was 0.46mm greater than for angiography. In the context of increments of balloon size (typically 1 mm for balloons used in the femoropopliteal segment), the difference in RVD between the IVUS and angiography and the limits of agreement of 1.56mm found in the Bland-Altman analysis (Figure 4.3) were likely to be clinically significant. A difference of 0.5mm between the measurements could easily result in a decision to increase the balloon size to the next size and a difference of 1mm, which is well within the limits of agreement, would be highly likely to increase the balloon size. This phenomenon was observed in this study with a difference of at least 0.5mm seen in 47% of cases and the balloon size being changed in 29.6% of cases in the treatment group.

The difference between IVUS and angiographic RVD was greater than that reported by Arthurs et al.(11), who found a non-significant difference in RVD measurements of 0.2mm in favour of IVUS. This study is probably the most comparable to the current trial because the equipment used was more similar (uni-planar digital angiography and 20MHz phased array IVUS) than the studies from the early to mid-1990s. The difference between IVUS and angiographic lumen measurements in the current trial is an important finding and it is therefore important to consider potential reasons why this there is a difference in this finding between the current study and that of Arthurs et al. (11).

There are at least two possible explanations for this difference. Firstly, in the study by Arthurs et al.(11) , IVUS and angiographic RVD measurements were taken at the same level in the artery whereas in the current study the measurements were obtained at the most normal appearing segment adjacent to the lesion based on each form of imaging. Obtaining the IVUS and angiographic RVD at the same level allows direct comparison of each imaging method in the same segment of vessel however this may not reflect actual clinical practice. In clinical practice the vessel appearances from each imaging method are likely to be assessed on their own merits, i.e. the RVD would be obtained from the most normal available segment as observed for each imaging

method. Earlier IVUS studies have found that normally appearing segments on angiography often have significant amounts of atherosclerotic plaques when imaged with IVUS(7, 13, 51, 69, 70, 74) and it is therefore likely that the most normal segments as seen by angiography and IVUS may not be in same location. The difference between the IVUS measurements found in the current study therefore may reflect absolute differences between the two imaging methods and differences in the segments chosen for the RVD measurement by each modality.

Secondly the angiographic measurement method used in the study by Arthurs et al.(11), was not defined. This is an important consideration as it has been demonstrated that the method of angiographic measurement has a significant effect on the measurement obtained with a range of almost 2mm in mean RVD between visual estimation, catheter tip calibration and calibration by radio-opaque ruler(41).

The median lesion length measured by IVUS was significantly longer than that measured by angiography. This is likely to be due to the ability of IVUS to identify plaque more accurately, as has been discussed above. Arthurs et al.(11), also found a significant difference in lesions length, however the lesions in that study were very short (mean length<20mm) and the actual difference between imaging methods was only 3mm. While this was statistically significant it is highly unlikely that such a difference would be clinically important. The difference in median lesion length of 20mm found in the current study is more likely to be of clinical importance as balloons and stents, up to about 120mm, increase in 20mm increments. Additionally, as demonstrated in the Bland-Altman plot in Figure 3.4, the IVUS measurement was more than 50mm longer than angiography in about a quarter of cases. A difference of this magnitude is highly likely to change the length of balloon or stent used even at the larger end of most product ranges. This finding suggests that treatment based on angiographic lesion length alone may result in under-treatment of the lesion.

It is striking that there was disagreement between IVUS and angiography in more than 80% of cases. The absolute number of types of disagreement was greater than this as more than one type of disagreement occurred in a quarter of cases. The most common types of disagreement were due to measurement of RVD and lesion length. The threshold for disagreement in RVD of 0.5mm was used because this was more than twice the error of the QVA calibration method and because, as discussed above, a difference of this magnitude was likely to result in a change to device size. The threshold of 20 mm was used for lesion length because it was it was likely to result in a change to the length of device used and the length of vessel treated.

4.3.3 Treatment modification due to IVUS findings

The treatment plan was modified in 78.8% of cases in the treatment group. In 83.7% of cases this was an increase in device size and/or treatment length. There is little quantitative data on how IVUS imaging alters treatment in the peripheral arteries, however earlier coronary experience has

suggested that treatments may be modified in 48-74% of cases (5, 105, 152). Buckley et al.,(143) found that IVUS identified inadequate iliac artery stent deployment in 40% of cases. These stents underwent additional dilatation resulting in larger stent diameters and improved patency at six years. Krishnan et al.(175), found an increase in the number of atherectomy passes performed when IVUS was used, resulting in smaller residual lumens at completion. Both these studies were retrospective and there has been a lack of prospectively collected data investigating whether this applies to a wider range of treatment technologies. The larger retrospective studies comparing angiography and IVUS have lacked information on changes to treatment(14, 15) and no conclusions were possible regarding the effect of IVUS on treatment and potential mechanisms for the improved outcomes reported in these studies.

A concern at the commencement of the trial was that there might be a learned effect from experience with IVUS which could lead to surgeons interpreting angiography measurements differently later in the study period. This might manifest in a reduction in the difference between the angiographic measurement of size and length and the size or length of the treatment used. This was assessed in the control group, as decision-making in this group was not directly affected by IVUS imaging, and no correlation was found in the difference between angiographic measurements and treatment size or treatment length over the time of the study. There was therefore no evidence of a systematic change over time that could be attributed to a learned effect.

4.3.4 Potential mechanisms for reduced rates of binary restenosis

Logistic regression analysis (Figure 1.10) suggested that the use of DCB was significantly less likely to result in binary restenosis. This was the only treatment variable with a significant odds ratio that could have been influenced by the IVUS findings. There was no difference in the use of DCB between the control and treatment groups suggesting that the access to the IVUS findings may not have changed the number of cases using DCB. There were, however, far fewer cases of binary restenosis after DCB treatment in the treatment group compared with the control group (Table 4.9). As discussed above, the most common modifications of treatment due to IVUS were an increase in balloon size or angioplasty length. This suggests that that IVUS influenced choice of DCB size and length may have been an important factor in the lower rate of binary restenosis.

It is certainly plausible that these two changes could have an effect on the performance of DCB angioplasty. DCB are primarily drug delivery devices that rely on transfer of paclitaxel to the vessel wall and this can only be accomplished when the wall is closely apposed to the intima(263). Complete wall apposition and coverage of the entire lesion are required for optimal drug delivery and suppression of neo-intimal hyperplasia(264, 265). Segment of lesions that are not treated during DCB therapy are termed geographic misses. This term is usually used in relationship to the use of multiple balloons when inadequate overlapping has occurred resulting in a zone that has received no drug. The IVUS findings from this study suggest that vessel diameter and lesion length

are both larger than is apparent on angiography. Reliance on angiographic assessment alone may result in a geographic miss due to the use of a balloon that is shorter than the lesion and it may also result in a different type of geographic miss when the balloon is not large enough to achieve full apposition, with portions of the vessel lumen surface receiving an inadequate dose of paclitaxel.

These observations are speculative and hypothesis generating as they cannot be proven from the data available. The power of the logistic regression analysis to identify predictors of restenosis was limited due to the small sample size and the conclusion related to DCB use should be considered tentative at this stage. At this stage, these results suggest that the odds of binary restenosis are reduced when DCB therapy is used. These findings are intriguing as they suggest a potential mechanism to explain the benefit from the use of IVUS. A larger trial is required with treatment subgroups of sufficient size to allow more definitive investigation of how the use of IVUS delivers improved outcomes. Such a trial should be multi-centre to improve the generalisability of the results, it should encompass a greater range of clinical end-points and be core-lab adjudicated to increase confidence in the imaging findings.

4.3.5 Limitations of the study

These are interim findings, as the one-year follow-up of the full target sample size had not yet been reached at the time of writing. Reporting at this time was required due to the constraints imposed by the timeframes imposed by the academic rules governing this thesis. Although the results to date are highly encouraging they should be treated with caution as preliminary until a more complete dataset has been collected.

A limitation of this study is that due to the geographical dispersal of participants, treadmill pressure testing was not able to be routinely performed on all participants with claudication after the index procedure and objective measures such as claudication onset time, pain free walking distance and maximum walking distance were not available. Quality of life assessment was also not performed as it was omitted from the original study design. This is an important limitation and represents a design failure of the study. There is therefore no data on changes to quality of life over the follow-up period.

IVUS imaging was performed primarily using the manual pullback method. Whilst this potentially limited the ability for quantitative data to be obtained from the IVUS imaging, it was a practical necessity due to the length of lesions included in the study and there is considerable evidence for its use in the peripheral vessels (12, 14, 68, 149, 150). The use of mechanical pullback, as used in coronary device trials, would have limited the trial to lesions <100mm in length(11) or added an impractical amount of time to procedures due to the need for multiple pullbacks in longer lesions. Restricting the length of lesions was rejected as it was felt that this would limit the generalizability

of the study's findings by not reflecting the type of cases seen in everyday clinical practice. It would have also created recruitment problems as it would have excluded the majority of cases treated in our unit. Whilst the extra time needed for multiple mechanical pullbacks could be justified in a trial setting, it was felt that this would be unlikely to be acceptable in everyday practice. This could have a negative effect on generalizability, as the trial would have been conducted using a technique that might not find wide clinical acceptance.

Due to the open nature of the inclusion criteria there was considerable heterogeneity of the sample. This can be viewed as both strength and as a weakness. The wide range of presentations, lesions types and treatments allowed the recruitment of a "real world" sample that was representative of the range of patients that may be seen in everyday clinical practice. Potentially the results of this study are therefore more generalizable. On the other hand, the heterogeneity of the sample cases resulted in a small number of cases for many of the treatments, limiting the ability to reach conclusions on the value of IVUS imaging for specific treatments with specific types of lesions. An alternative approach would have been to narrow the sample to a specific treatment and to lesions with particular characteristics. Whilst this approach has the advantage of potentially answering questions about the efficacy of the specified treatment in a well-defined situation it makes generalising the results of such a study to lesions and patients outside the study parameters less certain. The encouraging results in this study suggest that there would be value in undertaking more narrowly defined, targeted studies to further investigate the role of IVUS in specific treatments.

Whilst there were no statistically significant differences in any patient, lesion or treatment characteristics it must be acknowledged that both median lesion length (20mm) and median length of stented segments (30mm) were longer in the control group. These differences were not statistically significant and were smaller than the variance in these values as expressed by the IQR. This difference may therefore be a reflection of the relatively small sample size although the potential for this difference to have some clinical effect cannot be ruled out.

This was a single centre trial and so represents treatments performed by one group of interventionists. The protocols used and treatments attempted at this centre may differ from those offered by other interventionists and therefore the generalizability of these results may be less certain than for a multi-centre trial.

There was no independent monitor or review board to assess adverse events. Rigorous efforts were made to identify all major adverse events that occurred after the treatment by using multiple sources to identify events including interrogation of the state-wide health information system by the hospital epidemiology unit, review of individual patient records and accessing the records of patient who opted for private care.

Imaging was not core laboratory adjudicated and the angiographic and IVUS imaging results presented are the interpretation of the investigators only. Core laboratory adjudication was also not available for surveillance duplex ultrasound imaging due to resource constraints. Repeatability testing or central reading of these scans was not performed due to geographical and resource constraints. The aim of the study was to assess the effect of having IVUS imaging available at the time of treatment so the interpretation of the imaging and the actions taken based on this information are an intrinsic component of the study method. The lack of core laboratory adjudication therefore does not affect how the imaging was used at the time of each procedure but does limit the ability to assess how well the imaging was interpreted by the surgeons taking part in the study and the appropriateness of the imaging conclusions and treatments applied. Whilst there is the potential for bias in the results due to the lack of independent review of the procedural imaging, it should be noted that assessment of the primary outcome measure, i.e. binary restenosis, was obtained independently of the study investigators, with the duplex ultrasound surveillance examinations being performed by ultrasound providers blinded to the randomisation.

Recruitment was slower than anticipated and occurred over a longer period of time than originally planned. This was due to unit organisational changes that resulted in some femoropopliteal interventions being undertaken in the operating theatre, using mobile image intensifier equipment that did not support QVA software and therefore could not be included in the trial, and others being allocated to the interventional radiology team who were not participating in the trial, and due to a six-month pause in enrolment during this period due to serious illness to the candidate. The risk of changes in treatment practices as the duration of the study increased must be acknowledged. The randomisation processes should minimize this to some extent as any changes would affect cases enrolled into both groups. This phenomenon could potentially affect the generalizability of findings if there was a major shift in treatment methods over the time of the study, however this was not the case as all the treatment technologies used were available throughout the enrolment.

Testing of the QVA calibration method use in the current study suggests that it has a low degree of error but comparison with alternative angiographic measurement methods has not been performed and it is not known if there is variation between this method and alternative methods of angiographic measurement.

4.4 Summary

The interim findings from this RCT have found that participants treated using both IVUS and angiographic imaging guidance had a lower rate of binary restenosis at one year than those treated with angiographic guidance. There was no evidence of any additional risks from the use of IVUS, with no difference in peri-procedural complications, 30-day complications or major adverse events at one year.

There was some form of disagreement in findings between angiography and IVUS in most cases, with significantly larger RVD and lesion length found with IVUS. The treatment was modified in most of the cases where the surgeon had access to the IVUS findings, most commonly involving an increase in device size or treatment length.

The odds of restenosis were less in participants having DCB therapy and this appeared to be primarily in cases where the surgeon had access to the IVUS. This suggests that the use of IVUS may assist in optimising the use of DCBs. The reasons for this can only be speculative at this stage and a prospective study is required to investigate this.

5 ASSESSMENT OF THE PERFORMANCE OF CALCIUM SCORING SYSTEMS IN THE FEMOROPOPLITEAL ARTERIES USING IVUS IMAGING

5.1 Introduction and aims

Calcification of the arterial wall is a common finding in PAD and is seen in about half of patients having endovascular interventions (17, 178-180). Plain balloon angioplasty is considered to be less effective in patients with calcification, due to the associated problems of flow-limiting dissection and residual stenosis which result in the need for adjunctive or “bail-out” stenting (183-185, 198). Severe calcification, particularly concentric calcium, is also associated with vascular complications such as perforation (205). While DCBs have been shown to improve outcomes compared to plain balloon angioplasty(2, 3, 207), there is evidence that they are less effective in the presence of severe calcification, probably due resistance to dilatation and recoil related to loss of wall compliance and to impaired penetration of paclitaxel to the arterial wall(182, 184, 265). Adjunctive technologies such as scoring balloons(266, 267), atherectomy(268, 269) and more recently lithoplasty(205, 270) have been suggested as methods for improving results when severe calcification is present, however these treatments also add additional costs and potential risks to the procedures(169, 171, 271, 272). A key issue is therefore how to differentiate between cases with mild calcification, in whom plain or drug-coated angioplasty may be sufficient, and cases with severe calcification, in whom adjunctive technologies may potentially offer some benefit.

A wide variety of classification systems for scoring calcium severity in the femoropopliteal arteries have been reported with no standardised method yet established. In some studies the classification methods are clearly defined(165, 204, 205, 208), while in others no definitions are provided(3, 178, 180, 200, 201, 206, 207). Reporting of calcification in trials has been highly variable and ranges from detailed(178, 180, 202-206), to brief(3, 200, 201), to non-existent(2, 4).

Most scoring systems are based on angiography with one system incorporating CTA imaging (184). There is limited data on how well these scoring systems perform at classifying calcium severity and to date this has been limited to solely angiographic-based methods(210). There is no data comparing the performance of these systems and no data on inter-rater agreement and reliability of calcium scoring systems.

Intravascular ultrasound (IVUS) has been shown to be superior to angiography at identifying arterial calcification (9, 38) and is therefore an ideal modality for assessing the performance of calcium scoring systems. Currently there is only one study that has used IVUS for this purpose (210). In this study differences were seen between mild and severe grades for IVUS measurements of calcium length and arc of calcium.

The uncertainty regarding the comparative performance and reliability of classification systems creates uncertainty about how comparable results of calcium assessment are across trials(273) and therefore hampers the application of evidence from trial results to clinical practice(274).

5.1.1 Study aims

The aim of this study was to assess whether calcium scoring systems were able to categorise calcium severity, according to IVUS calcium parameters, and to assess the agreement and reliability between these systems.

5.1.2 Research questions

This chapter will present and discuss the findings from research performed to answer the following research question related to the aims stated in section 5.1.1:

Research question 2 (RQ2): Are IVUS calcium parameters different between grades of severity of calcium scoring systems and how reliable are these systems at classifying severity in the femoropopliteal arteries?

5.1.3 Hypothesis

The hypothesis related to the aims and research question was:

Hypothesis 2: There will be a significant difference in the length of calcium and arc of calcium, measured by IVUS, between severe and mild grades of calcium for all the calcium scoring systems, and there will be good agreement and reliability of classifications between scoring systems.

5.2 Methods

5.2.1 Study sample selection

A sample of 60 consecutive cases was retrieved from the IVUS RCT database for analysis. The inclusion and exclusion criteria for subjects enrolled in the IVUS RCT are detailed in Chapter 3 of this thesis.

5.2.2 Angiographic and CTA image analysis

Two raters assessed the cases for the presence of calcium. Both raters were vascular surgeons holding Fellowships of the Royal Australian College of Surgeons (Vascular) and had been trained in, and were regularly performing, peripheral endovascular interventions. Each rater had a one-on-one training session with the candidate on the method for assessing lesion and calcium parameters and the calcium scoring systems being evaluated. They then performed ten trial cases followed by a review session with the candidate to check that assessment interpretation and data entry was consistent with the study design. Once this had been confirmed, scoring of the 60 cases was able to commence. The raters were blinded to the patient data, clinical presentation, procedural information and the outcomes of the procedures. They were also blinded to each other's results to ensure independent assessment of lesion characteristics.

Angiographic and CTA Images were viewed on the hospital PACS system (Vue RIS v11.0.14.35, Carestream Health, Rochester, New York) or on the Intelliviewer PACS system (Intelliviewer 4-9-1-P78, Intelerad Medical Systems, Montreal, Canada) if the CTA was performed outside the hospital. The raters were asked to view the angiographic and CT image files only, and not to view the radiology report and referral request form to remain blinded to the clinical presentations, procedural information and diagnostic reports. This was straightforward as these files are held separately to the imaging files in both PACS systems and so did not need to be opened when the images were assessed.

Each rater was asked to assess each set of angiographic images and record the following features:

- presence of calcification
- estimated lesion length (in mm)
- estimated length of the calcium within the lesion (in mm)
- whether the calcium was present for <50% or ≥50% of the lesion length
- distribution of the calcium around the wall, i.e. unilaterally or bilaterally. Bilateral calcium was defined as present on both sides of the artery at the same location.

Lesion length was estimated from the DSA contrast enhanced images, with the assistance of the radio-opaque ruler, based on the rater's assessment of the proximal and distal extent of the lesion.

Angiographic assessment of calcium was performed by viewing the pre-treatment un-subtracted angiographic image prior to opacification with contrast. In general, pre-treatment angiographic imaging was performed using single plane imaging. The use of orthogonal planes was not required in the department procedural protocols or for the IVUS RCT. Calcium length was estimated, with the assistance of the radio-opaque ruler, based on the proximal and distal extent of the largest continuous length of calcium seen within the lesion. A continuous length of calcium was defined as calcium with gaps between deposits of less than 5mm.

CTA scans were able to be assessed if it was performed within the six months prior to the endovascular procedure and there was no other endovascular or surgical treatment performed on the target femoropopliteal artery in the intervening time. The CTA images were windowed to allow clear differentiation between contrast-filled lumen and calcium. The CTA imaging from the origin of the SFA to the tibial bifurcation was assessed for the presence of calcium and the distribution of calcium around the artery circumference, using the method described by Fanelli (184). Frames containing calcium were identified and the distribution of calcium around the wall was visually assessed by each rater. The calcium distribution was categorised according the number of quadrants of the wall containing calcium. The frame with the maximum number of quadrants containing calcium was identified and the number of quadrants was recorded. Calcium volume software was not used as this technology is not used in the calcium scoring systems under investigation in this study.

5.2.3 IVUS image analysis

Pre-treatment IVUS imaging files were assessed for the presence of calcium using the same frame sampling methodology employed by the Atherosclerosis Imaging Core Laboratory (AICL), South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia. Briefly, this methodology entailed sampling frames every 2mm throughout length of the IVUS pullback (please refer to Chapter 7 for a detailed description of this method). IVUS image assessment was performed by the candidate, blinded to the results of the angiographic grading by the vascular surgeon raters, using IVUS review software (echoPlaque 4.3, INDEC Medical Systems, Los Altos CA).

The sampled frames were assessed for the presence of calcium and the number of

quadrants containing calcium. The presence of a calcified lesion was confirmed by the presence of calcium in three consecutive frames (equivalent to at least 5mm length)(160). A lesion less than 4mm long with an arc of calcification <45° was considered to represent "spotty" calcification(275) and was not classified as a calcific lesion for the purposes of this study. A calcified segment was considered continuous if the gap between frames containing calcium was no more than three frames (equivalent of 5mm). This definition was used to ensure consistency with the angiographic analysis. The length of the longest calcium lesion was calculated by multiplying the number of sampled frames by 2mm, i.e. a calcium lesion that extended over 17 sampled frames represented a measurement of 34mm. The arc of calcification was measured in degrees and the number of quadrants of calcium was recorded for the frame with maximum stent of calcium around the wall.

5.2.4 Calcium scoring

Each rater generated a calcium score for each case using the DEFINITIVE Ca++(161), PACSS(17), PARC(162) and Fanelli(184) systems(Table 5.1). For the first three methods, a score was generated from the angiographic assessment of calcium length and distribution of calcium around the wall based on the authors' definitions. The calcium score for the Fanelli system was generated by using the calcium length measured by angiography and the number of quadrants containing calcium assessed by CTA.

A single score for each system in each case was generated by combining the raters scores using a consensus process. When there was agreement in the calcium severity grade between raters this was recorded as the grade for the case. When there was disagreement in the calcium grade the case was reviewed by a third rater, trained in the method as described above and blinded to the results of the original two raters, who assessed the images in which there was disagreement and produced a third score. If two out of three scores agreed, this became the final score for the case. If all three scores were different a consensus meeting between the raters was held to reach a final score.

Table 5.1 Peripheral arterial calcium scoring systems

DEFINITIVE Ca**(161)	None/mild	Not defined	
	Moderate	radiopacities on one side of arterial wall or less than 1 cm of length	
	Severe	radiopacities on both sides of arterial wall and extending more than 1 cm of length	
PACSS(17)	0	no visible calcium at target lesion site	
	1	unilateral calcification<5cm: a)intimal, b)medial, c)mixed	
	2	unilateral calcification ≥5cm: a)intimal, b)medial, c)mixed	
	3	bilateral calcification<5cm: a)intimal, b)medial, c)mixed	
	4	bilateral calcification ≥5cm: a)intimal, b)medial, c)mixed	
Fanelli(184)	1a	0-90°	<3cm length
	1b		≥3cm length
	2a	90-180°	<3cm length
	2b		<3cm length
	3a	180-270°	<3cm length
	3b		≥3cm length
	4a	270-360°	<3cm length
	4b		≥3cm length
PARC(162)	Focal	<180° circumference (1 side of vessel) and less than one-half of total lesion length	
	Mild	<180° circumference (1 side of vessel) and greater than one-half of total lesion length	
	Moderate	≥180° circumference (both sides of vessel at same location) & less than 1/2 of total lesion length	
	Severe	≥180° circumference (both sides of vessel at same location) and greater than one-half of total lesion length	

To allow comparison between systems, the PACSS, PARC and Fanelli classification systems was condensed into simplified form with three categories (no calcium, mild and severe) to match the number of categories used in the DEFINITIVE Ca++ system. Simplification was performed by grouping all categories with bilateral calcium (or 3-4 quadrants in the case of the Fanelli system) into a single severe category with all other categories of calcium grouped as mild.

5.2.5 Statistical Analysis

Continuous data was reported as mean (SD) or median (IQR) depending on whether the distribution approximated normality. Categorical data was presented as n (%). Normality of distribution was assessed visually and by the use of Shapiro-Wilks tests of normality. Testing for difference of continuous data between two groups was performed using the independent sample t-test or the Mann-Whitney U test depending on whether the distribution approximated normality. Testing of difference of continuous data between more than two groups was performed using ANOVA or the Kruskal Wallis test depending on whether the distribution approximated normality, with post hoc analysis to identify the difference between specific pairs using Dunn's pairwise test (with significance adjusted using the Bonferroni method)(276). Testing of difference between groups for categorical data was performed using the chi-square test or Fisher's exact test (for dichotomous variables when a result of ≤5 was expected).

Agreement of continuous data was assessed using the ICC and by the use of Bland-Altman plots and limits of agreement analysis (261), for data that approximated normality(261, 262). Testing of agreement of categorical data was performed by calculating the observed agreement, the positive agreement and the negative agreement. These were calculated using the following equations: observed agreement = (a + d)/N, positive agreement (specific agreement on positive rating) = 2a/(2a+b+c), negative agreement (specific agreement on negative rating) = 2d/(2d+b+c), derived from 2x2 contingency table (277, 278).

Testing of reliability of categorical data was performed using Cohen's Kappa (κ) statistic, using unweighted κ for dichotomous data and linear weighted κ for ordinal data with more than two categories(279-282). Interpretation of the level of agreement for Kappa values were based on the recommendations of Mandrekar(279), with the following categories: <0.40 poor, 0.41-0.75 fair to good, and >0.75 excellent agreement.

Significance was set at p=0.05 unless otherwise stated.

5.3 Results

5.3.1 Patient demographics and angiographic, IVUS and CTA assessment of lesion and calcium characteristics

Sixty patients were included in the study population and demographics were consistent for patient being treated for PAD, with a mean age of 74.5 years and 73.3% males (Appendix 5, Table A5.1). Forty percent of patients presented with CLI, 35% had diabetes mellitus, 56.7% had a GFR <60ml/min, 62.7% of cases involved the popliteal artery and 30% of arteries were occluded. The median lesion length by angiography was 142.5mm.

Lesion and calcium parameters for angiography and IVUS are presented in Table 5.1. The prevalence of calcification according to IVUS imaging was 90.0%. In 13 cases calcification seen on IVUS was not identified on angiography. There were no cases of calcium seen on angiography not seen on IVUS. The observed agreement for the detection of calcium between the two modalities was 0.78, positive agreement was 0.86 and negative agreement was 0.48. The sensitivity of angiography for detection of calcification, using IVUS as the reference standard, was 75.9% (95% CI: 62.4% to 86.5%), specificity was 100% (95% CI: 54.1% to 100.00%), positive predictive value (PPV) was 100% (95% CI: n/a) and negative predictive value (NPV) was 31.6% (95% CI: 22.3% to 42.6%).

Comparison of IVUS and angiographic parameters showed that there were significant differences between angiography and IVUS for all continuous and categorical parameters except for lesion length.

Table 5.2 Comparison of vessel parameters between angiographic and IVUS

	Angiography (n=60)	IVUS (n=60)	Significance (p)
Lesion length (mm)	142.5 (178)	150 (218)	0.106*
Calcium present	41	54	0.001†
Calcium length (mm)	40 (80)	63 (107)	0.013*
Calcium length ≥ 50% of lesion length	23	31	<0.001‡
Bilateral or 3-4 quadrant distribution of calcium around the wall	28	37	0.001‡

Median (IQR), *Mann Whitney U test, †Fishers exact test, ‡Chi-square test

The ICC for lesion length measurements by angiography and IVUS was 0.728 (95% CI:0.502-847, p<0.001) and for calcium length by angiography and IVUS was 0.783 (95% CI:0.505-892, p<0.001). Bland Altman agreement plots were generated for both lesion length and calcium length (Figure 5.1). Means and limits of agreement were not plotted for either parameter due to the lack of

normality of the distributions. There was a bias toward longer measurements for IVUS for both lesion length (32.5mm, IQR=89mm) and calcium length (24mm IQR=68mm).

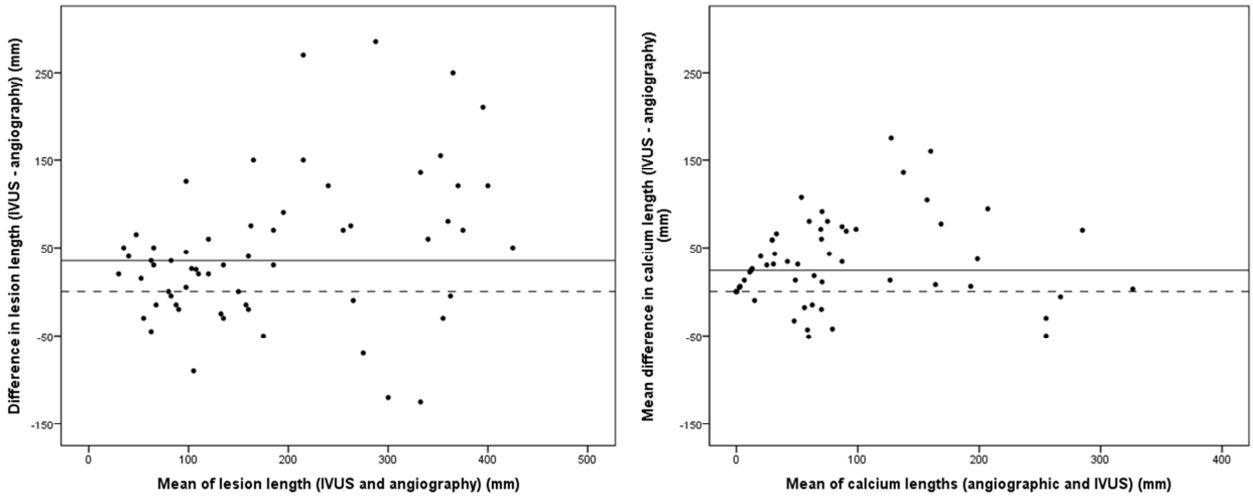

Figure 5.1 Bland Altman agreement plots of IVUS and angiographic lesion length measurements and calcium length measurements. Solid line: median, dashed line: 0mm

There were low levels of observed agreement between IVUS and angiography for the proportion of the lesion containing calcium (observed agreement=0.53) and for the distribution of calcium around the wall (observed agreement=0.52).

The difference in median maximum arc of dissection was compared for angiographic categories of calcium distribution (Figure 5.2). There was a significant difference in mean ranks for the maximum arc of calcification between the categories ($p<0.001$, Kruskal Wallis test). Post-hoc Dunn's pairwise testing found that there was a significant difference in mean ranks between cases with no calcium and cases with calcium on two sides of the artery ($p<0.001$) but no evidence of a difference in mean ranks between cases with no calcium and calcium on one side of the artery or for calcium seen on one side or both sides of the artery.

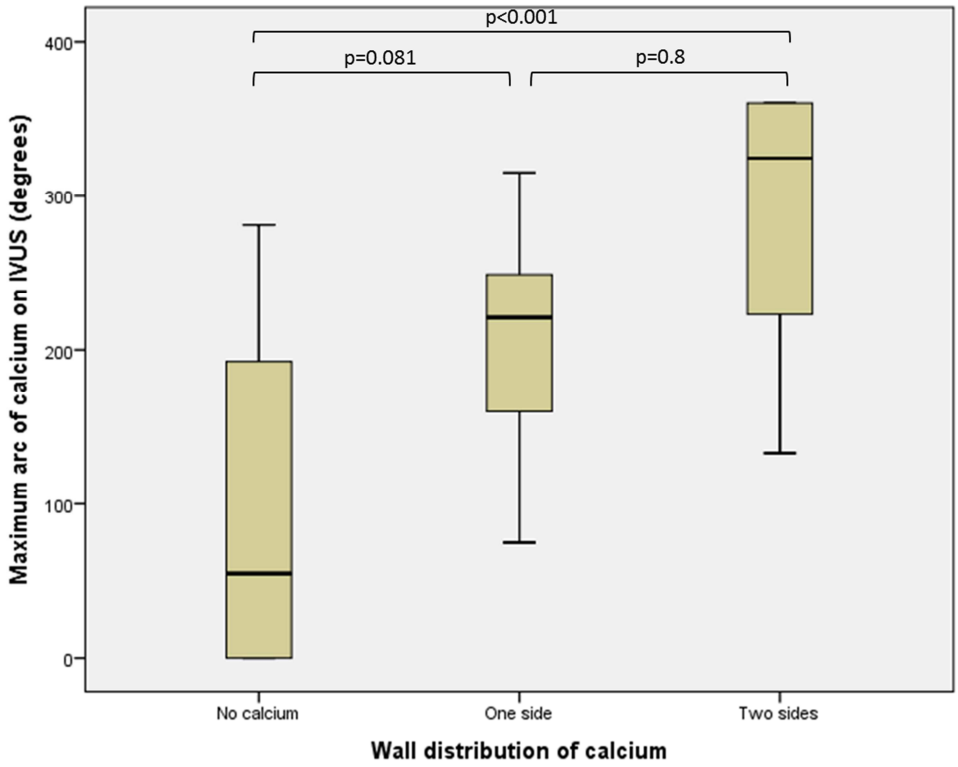

Figure 5.2 IVUS maximum arc of calcium for categories of angiographic calcium wall distribution. Rank differences in median length are displayed

CTA imaging was available in 47 cases. In 12 cases there was no CTA performed within six months of the angiogram and in one case the CTA was uninterpretable due prosthetic artefacts. In three cases calcium, identified by IVUS, was not identified by CTA. There were no cases of calcium seen on CTA that were not seen on IVUS. The sensitivity of angiography for detection of calcification, using IVUS as the reference standard, was 95.5% (95% CI: 84.5% to 99.4%), specificity was 100% (95% CI: 29.2% to 100.00%), PPV was 100% (95% CI: n/a) and NPV was 60.0% (95% CI: 27.9% to 85.3%). Agreement for the detection of calcium was very high between IVUS and CTA, with an observed agreement of 0.96, positive agreement of 0.98 and negative agreement of 0.75. There was a significant difference in the maximum number of quadrants containing calcium for each case between IVUS and CTA, with number of quadrants containing calcium being higher on IVUS in 22 cases and higher on CTA in two cases ($p<0.001$, chi-square test). There was an observed agreement 0.49 and moderate reliability between modalities of $\kappa=0.549$ (95% CI: 0.390-0.703).

5.3.2 IVUS calcium parameters in relation to grades of severity for calcium scoring systems

IVUS parameters for each grade of calcium severity are presented for the DEFINITIVE Ca++ (Table 5.3), PACSS (Table 5.4), PARC (Table 5.5) and Fanelli (Table 5.6) scoring systems in their original forms. There were significance differences in rank between grades of severity for calcium length and maximum arc of calcium for all four systems.

Box and whisker plots of the five-number summaries for calcium length and maximum arc of calcium, measured by IVUS, in all grades of the four scoring systems are presented in Figures 5.3 and 5.4. There was a general trend seen for an increasing magnitude in both length and maximum arc of calcium as the grade of calcium severity increased across the scoring systems. Interquartile ranges and minimum-maximum ranges tended to be wider for maximum arc of calcium compared to length of calcium. Significant differences, using post-hoc Dunn's tests (applying the Bonferroni adjustment), were found for length and maximum arc of calcium between pairs of grades involving the no calcium category and various categories of calcium severity in all four scoring systems, but there were no significant differences present between any other pairs of severity grades.

Table 5.3 IVUS calcium parameters for DEFINITIVE Ca++ scoring system (n=60)

	None	Moderate	Severe	p*
Number of cases	19	13	28	
Lesion length (mm)	120 (80)	130 (215)	240 (295)	0.012
Reference vessel lumen area (mm^2)	18.9 (9.0)	21.1 (6.0)	22.8 (14.4)	0.296
Calcium length (mm)	13 (40)	76 (70)	129 (156)	<0.001
Maximum arc of calcium (°)	55 (205)	221 (105)	324.5 (144)	<0.001

Median(IQR), *Kruskal Wallis test

Table 5.4 IVUS calcium parameters for PACSS scoring system (n=60)

	0	1	2	3	4	p*
Number of cases	19	8	5	5	23	
Lesion length (mm)	120 (80)	120 (240)	180 (190)	120 (317)	240 (280)	0.042
Reference vessel lumen area (mm^2)	18.8 (9.0)	20.8 (10.0)	21.1 (12.3)	18.5 (9.8)	26.0 (16.4)	0.196
Calcium length (mm)	13 (40)	60.5 (64)	104(134)	100 (76)	168 (170)	<0.001
Maximum arc of calcium (°)	55 (205)	210.5 (108)	237 (146)	190 (223)	331 (108)	<0.001

Median(IQR), *Kruskal Wallis test

Table 5.5 IVUS calcium parameters for PARC scoring system (n=60)

	0	Focal	Mild	Moderate	Severe	p*
Number of cases	19	7	6	12	16	
Lesion length (mm)	120 (80)	165 (248)	120 (230)	400 (303)	240 (225)	0.031
Reference vessel lumen area (mm^2)	18.8 (9.0)	20.2(12.7)	21.0 (8.5)	18.1 (8.6)	29.4 (12.8)	0.016
Calcium length (mm)	13 (40)	107.5 (265)	53 (72)	85.5 (57)	208 (107)	<0.001
Maximum arc of calcium (°)	55 (205)	210.5 (139)	230 (108)	223 (141)	360 (43)	<0.001

Median(IQR), *Kruskal Wallis test

Table 5.6 IVUS calcium parameters for Fanelli scoring system (n=47)

	0	1b	2a	2b	3b	4b	p*
Number of cases	15	4	3	10	5	10	
Lesion length (mm)	120 (80)	235 (238)	120	355 (340)	350 (245)	240 (165)	0.064
Reference vessel lumen area (mm^2)	18.5 (9.5)	24.5 (12.0)	20.0	24.2 (8.6)	18.5 (13.3)	29.7 (16.7)	0.203
Calcium length (mm)	13 (26)	64 (57)	59	110 (112)	125 (115)	223.5 (167)	<0.001
Maximum arc of calcium (°)	55 (205)	209.5 (103)	237	204.5 (101)	290 (160)	360 (32)	<0.001

Median(IQR), *Kruskal Wallis test, Note: there were no cases in grades 1a, 3a and 4a

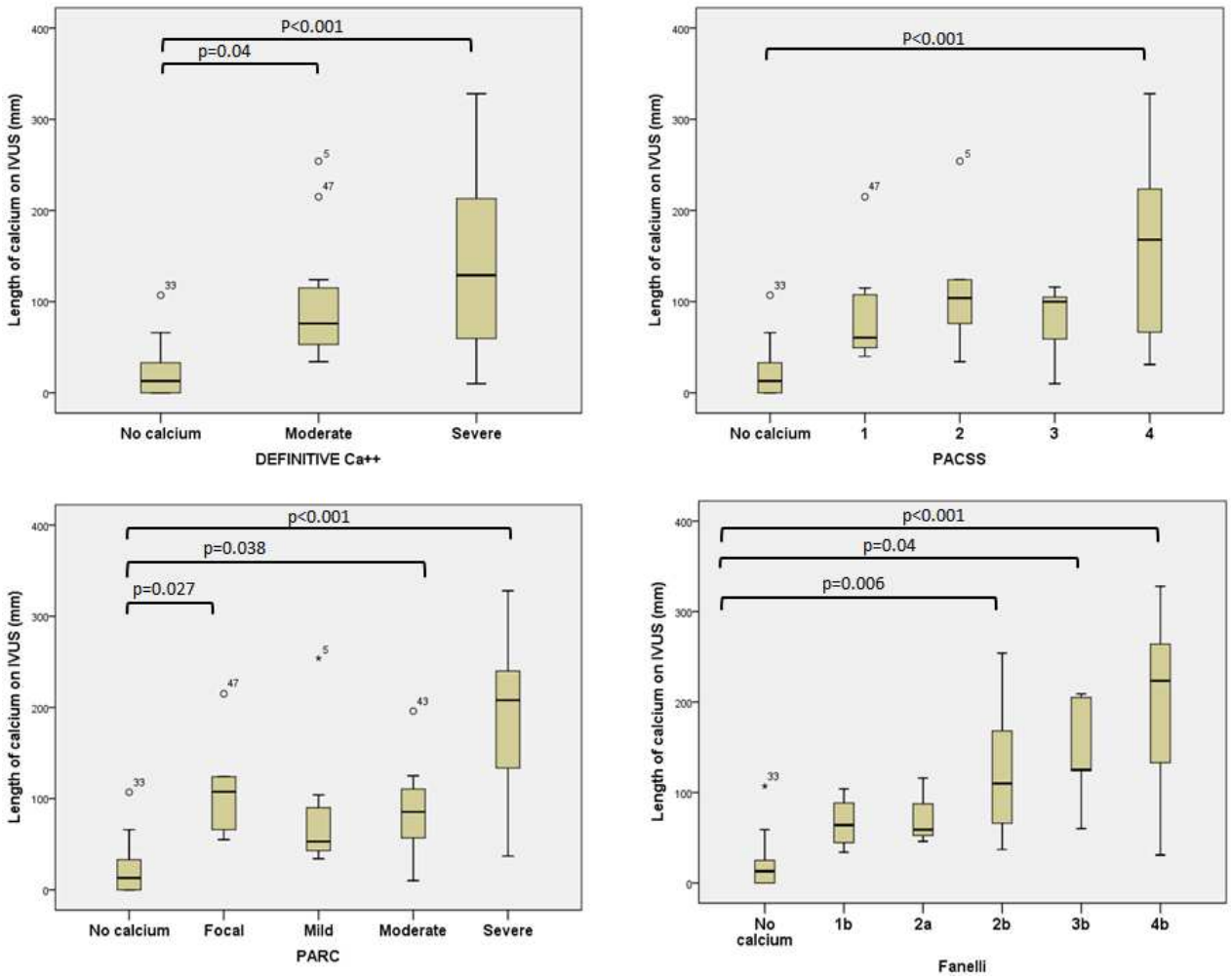

Figure 5.3 IVUS calcium length for categories of calcium severity for the DEFINITIVE Ca++, PACSS, PARC and Fanelli systems. Significant rank differences in median length are displayed

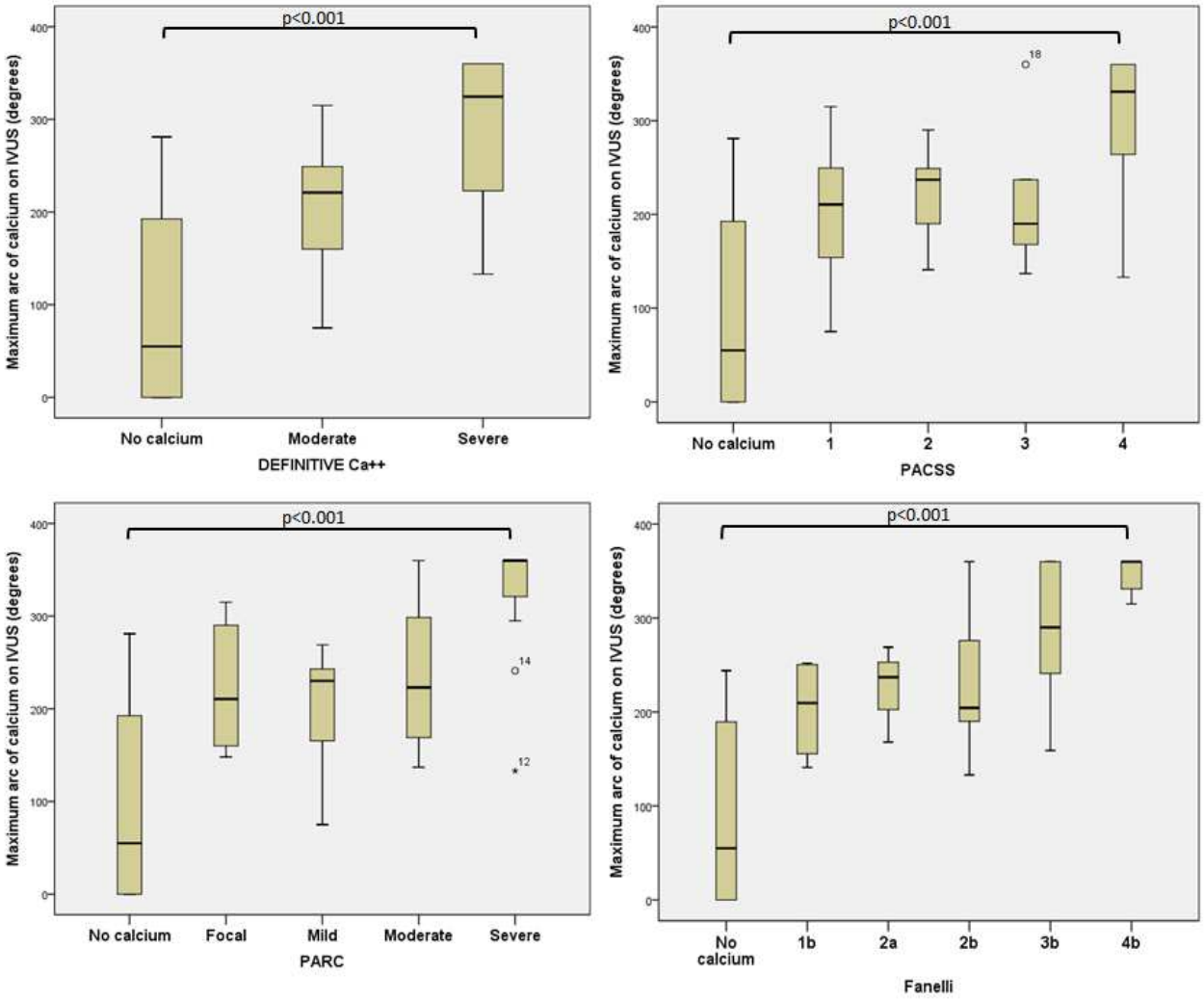

Figure 5.4 IVUS calcium arc for categories of calcium severity for the DEFINITIVE Ca++, PACSS, PARC and Fanelli scoring systems. Significant rank differences in median length are displayed

When simplified to grades of “no calcium”, “mild calcium” or “severe calcium”, on the basis of unilateral or bilateral calcium, complete agreement was found between the DEFINITIVE Ca+, PACSS and PARC systems. The results for IVUS lesion and calcium parameters according to simplified grades of severity for these three systems were therefore the same as those presented for the DEFINITIVE Ca++Table in 5.3. The results for the simplified Fanelli system are presented in Table 5.7. Significant differences in rank were present between grades of severity for lesion length, calcium length and maximum arc of calcium (Kruskal Wallis test).

Table 5.7 IVUS calcium parameters for simplified Fanelli scoring system (n=47)

	None	Moderate	Severe	p*
Number of cases	15	17	15	
Lesion length (mm)	120 (80)	290 (312)	240 (210)	0.010
Reference vessel lumen area (mm^2)	18.9 (9.0)	22.7 (8.6)	22.7 (16.6)	0.163

Calcium length (mm)	13 (40)	98 (70)	209 (116)	<0.001
Maximum arc of calcium (°)	55 (205)	209 (92)	360 (45)	<0.001

Median(IQR), *Kruskal Wallis test

Box and whisker plots of the five-number summaries for calcium length and maximum arc of calcium, measured by IVUS, in all grades of the DEFINITIVE Ca++/simplified PACSS/simplified PARC systems (as displayed for DEFINITIVE Ca++ in Figures 5.3 and 5.4) and the simplified Fanelli system are presented in Figures 5.5, with the full results of all post-hoc Dunn's test displayed. Significant differences, using post-hoc Dunn's tests (applying the Bonferroni adjustment), were found for both length and maximum arc of calcium between the no calcium and mild calcium grades and the no calcium and severe calcium grades for the DEFINITIVE Ca++/simplified PACSS/simplified PARC systems. No difference was found between the mild and severe calcium grades for these systems. In the Fanelli system, there were significant differences found for length of calcium between the no calcium and mild calcium grades and the no calcium and severe calcium grades, but there were no significant differences between the mild and severe calcium grades. For maximum arc of calcium, there were significant differences found between all pairs of grades, including between mild and severe grades of calcium severity.

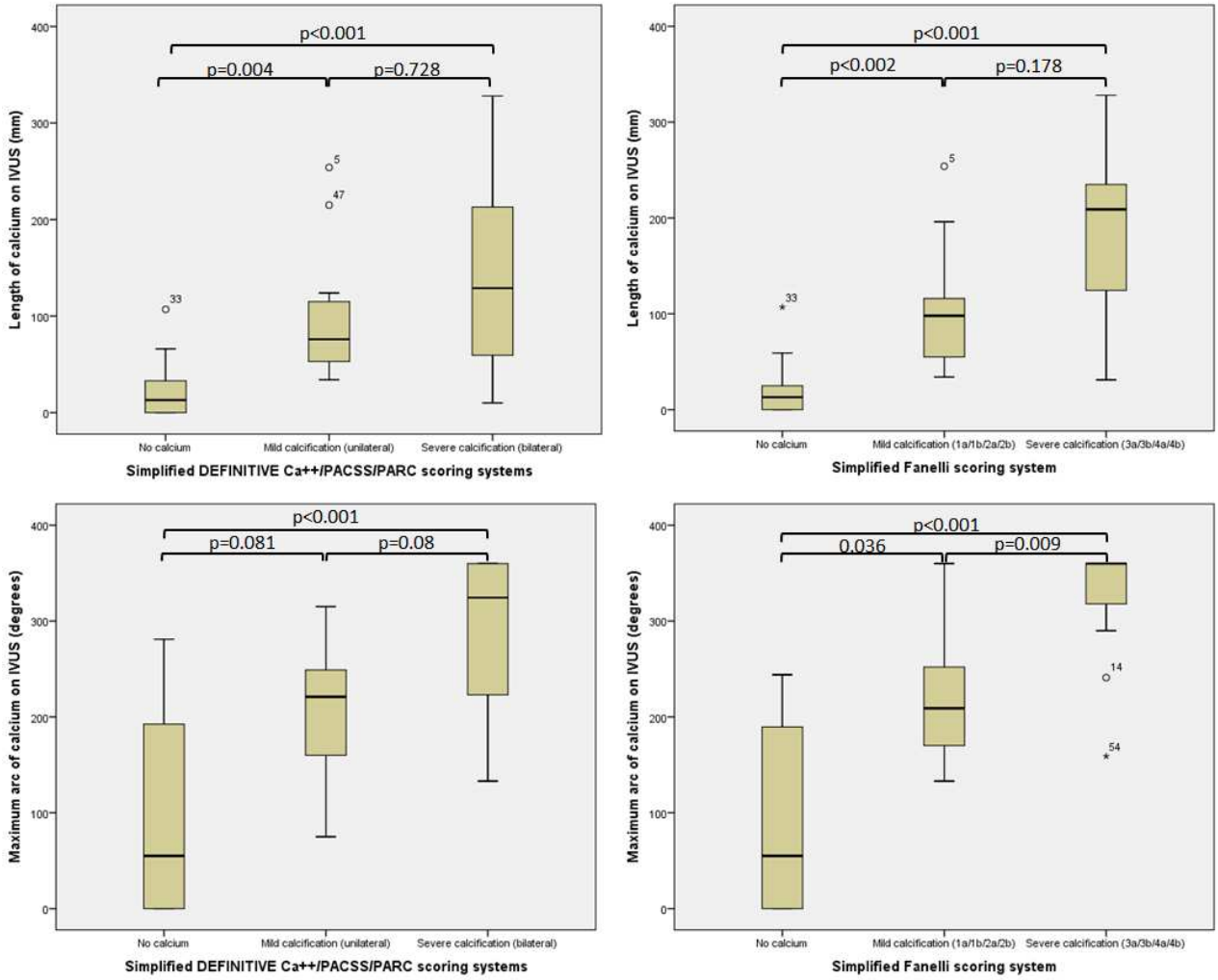

Figure 5.5 Calcium length and maximum arc of calcium, by IVUS, for DEFINITIVE Ca++/simplified PACSS/simplified PARC systems and the simplified Fanelli scoring system. Rank differences between pairs are displayed

5.3.3 Agreement and reliability between simplified scoring systems

There was complete agreement for the DEFINITIVE Ca++, PACSS and PARC scoring systems (19 cases of no calcium, 13 cases of mild calcium and 28 cases of severe calcium) when these were simplified into three categories.

Comparison of the DEFINITIVE Ca++/simplified PACSS/simplified PARC scoring systems and simplified Fanelli system found an observed agreement of 0.75 (Table 5.8). When allocation into the severe category was considered, for cases with calcium present, the positive agreement was 0.68 and the negative agreement was 0.54. There was good reliability between the two systems for grading of calcium, κ=0.726 (95% CI:0.585-0.867).

Table 5.8 3x3 contingency table comparing the Fanelli system with the DEFINITIVE Ca++/PACSS/PARC scoring systems (when severe calcium is defined as bilateral/3-4 quadrant calcium)

		Fanelli scoring system (modified)			
		No calcium	Mild calcium	Severe calcium	Total
DEFINITIVE Ca++ ++/PACSS/PARC scoring system (modified)	No calcium	15	0	0	15
	Mild calcium	0	7	2	9
	Severe calcium	0	10	13	23
	Total	15	17	15	47

5.3.4 Inter-rater agreement and reliability of angiographic results and calcium score systems

5.3.4.1 Angiographic results between raters

There was no difference seen in estimation of lesion or calcium length measurements between the two raters but there was a significant difference between the raters for the presence of calcium, the proportion of the lesion containing calcium and the location of calcium on the artery wall (Appendix 5, Table A5.2)

The IIC between raters for lesion length measurements was 0.813 (95% CI:0.706-0.884, p<0.001) and for calcium length was 0.672 (95% CI:0.502-791, p<0.001). Bland Altman limits of agreement analysis could not be performed due to the lack of approximation to normality of the distributions. There was a bias toward longer length measurements for Rater 2 compared with Rater 1of 10mm (IQR=63) but no evidence of bias for calcium length.

The results of kappa testing of categorical angiographic parameters for the two raters found fair to moderate agreement for all parameters: κ=0.429 (95% CI:0.195-0.663) for the presence of

calcium, κ=0.522 (95% CI:0.359-0.686) for the proportion of the lesion containing calcium and κ=0.414 (95% CI:0.238-0.590) for the number of sides of the artery containing calcium.

5.3.4.2 Calcium scoring agreement and reliability between raters

2x2 contingency tables comparing calcium grading by two raters for the DEFINITIVE Ca++, PACSS, PARC and Fanelli scoring systems are presented in Appendix 5, Tables A5.3 to A5.6. For all the scoring systems, Rater 2 systematically scored a greater number cases to a higher grade than Rater 1. The observed agreement and kappa statistic of each scoring system for the two raters are presented in Table 5.9. The observed agreement between raters ranged from 0.45 to 0.55, with the DEFINITIVE Ca++ system having the highest agreement and the Fanelli system having the lowest agreement. There was fair to moderate reliability (ranging from κ=0.414 to κ=0.540) between raters for all of the scoring systems.

Table 5.9 Observed agreement and weighted kappa statistics for two raters of four calcium scoring systems

	Observed agreement (95% CI)	Weighted κ (95% CI)
DEFINITIVE Ca++	0.55 (0.42-0.68)	0.414 (0.238-0.590)
PACSS	0.47 (0.34-0.60)	0.461 (0.301-0.621)
PARC	0.52 (0.39-0.65)	0.474 (0.308-0.639)
Fanelli	0.45 (0.30-0.60)	0.540 (0.381-0.700)

5.4 Discussion

5.4.1 IVUS calcium parameters in relation to severity grading by scoring systems

Despite the widespread use of calcium scoring systems to identify and categorise the severity of vessel wall calcification, there is little data regarding how well the classifications used in calcium scoring systems agree with the actual severity of calcium present. This study found that there was a trend for lesions of greater severity, as defined by IVUS parameters, to be allocated into more severe grades for all the scoring systems. There was a considerable range present for IVUS parameters in many of the severity grades, particularly for the maximum arc of calcium, results and marked overlap of results between grades. No difference in lesion severity between grades of severity was found for any of the four scoring systems in their original forms, with the only differences being between the no calcium grade and various grades containing calcium. Even after simplification of the scoring systems, a significant difference was only present between mild and severe calcium for the maximum arc of calcium for the Fanelli system.

In contrast to the current study, Yin et al.(210), in the only other study that has used IVUS to assess the performance of calcium scoring systems, found a significant difference in calcium length between mild and severe calcification for the DEFINITVE Ca++ and PACSS systems, and a significant difference in both length and arc of calcium between mild and severe calcification for the PARC system. Comparison of box and whisker plots between the current study and that of Yin et al.(210), suggests that there was less range of measurements in the results of Yin et al, particularly for calcium length, and this may have contributed to the finding of significant differences between grades of calcium severity. There were technical differences between the two studies that may have contributed to this difference, with Yin et al.(210), reporting shorter lesions (median lesion length was 45mm vs 142.5mm in the current study, routine use of imaging in orthogonal planes (compared to single plane in the current study) and the use of core laboratory analysis. In addition, Yin et al, did not simplify the grades of the scoring systems in the same way as was performed in the current study. They did modify the grades for the PACSS and PARC systems, however in contrast to the current study they did this by combining the two mildest grades of calcium and retained the moderate and severe grades as separate categories. The moderate grade had a lower median calcium length in both the PACSS and PARC systems and lower median arc of calcium in the PARC system. Combining moderate and severe grades for these systems would probably have resulted in smaller median measurements and this may have affected the result of differences testing between mild and severe grades.

The wide ranges present in the current study for calcium length and arc of calcium in severity grades significant may be a reflection of the significant differences found in most lesion and calcium parameters between angiographic and IVUS imaging as demonstrated in Table 5.2 and Figure 5.1. Unfortunately, this data was not reported by Yin et al.(210), so it is impossible to

assess how well angiography and IVUS agreed in that study and how this might relate to the significant differences in IVUS parameters between mild and severe grades

Novel aspects of this current study, in comparison to that of Yin et al.(210), was the simplification of the scoring systems into forms that allowed direct comparison between systems and the addition of the Fanelli scoring system. While Yin et al, simplified the PACSS and PARC systems, this was not in a form that allowed direct comparison between the three systems that were studied. When scoring systems were simplified in the current study, the results for the DEFINITIVE Ca++, PACSS and PARC systems were exactly the same, with no difference found in length or arc of calcium between mild and severe grades. A significant difference was found for the maximum arc of calcium between mild and severe grades for the simplified form of the Fanelli system, suggesting that this system may be better at identifying lesions with more severe calcification around the wall than the angiography-based systems. This is a potentially important finding as validation studies suggest that the distribution of calcium around the wall is probably a more important predictor of restenosis than the length of calcium(182, 209, 283). The poor performance of angiography at characterising calcium has been clearly identified in the past (9, 38) and significant differences were seen between IVUS and angiography for most parameters in the current study. The superior performance of the Fanelli system at categorising lesion severity compared to the angiography-bases systems may reflect the superior sensitivity of CTA (CTA sensitivity of 95.5% vs. 75.9% for angiography in the current study) and better agreement with IVUS (positive agreement of CTA 0.98 vs.0.86 for angiography).

While there was complete agreement between the DEFINITIVE Ca++, PACSS and PARC systems there was considerable disagreement between these systems and the simplified Fanelli systems, with a positive agreement for severity of calcium of 0.68 (indicating disagreement in 32% of cases with calcium present) and moderate reliability of κ=0.62. Yin et al.(210), did not directly compare the allocation of cases to grades between the DEFINITIVE Ca++, PACSS and PARC systems, but also found a high level of agreement for classification of severe calcium (as defined by bilateral distribution) with the PACSS and PARC systems having was complete agreement for cases with bilateral calcium (PACSS grades 3/4 and PARC moderate/severe) and disagreement in only three cases with the DEFINITIVE Ca++ system.

5.4.2 Inter-rater agreement and variability

Evidence of considerable variability in the performance of the scoring systems between raters was found. The level of observed agreement between raters was disappointing for all four systems, ranging from 0.45 to 0.55. This means that the two raters disagreed in allocating calcium grades in 45% to 55% of cases. The reliability between raters was fair to moderate, with the kappa statistic ranging from 0.414-0.540, indicating that that was considerable variability in how cases were categorised between the raters.

There do not appear to be any previous studies reporting inter-rater reliability for calcium scoring in the peripheral arteries. These results raise significant concerns regarding reliability of these scoring methods. Studies using core laboratory adjudication of calcium scoring have not reported reliability (182, 210), however it would be useful for this information to be available in order to compare with the results of current study. Efforts were made to ensure that raters were assessing imaging in the same way including a thorough training process prior to undertaking reading of the study cases. Differences in image interpretation due to differences in training are also unlikely as the raters trained at the same institutions within five years of one another. This result suggests that there may be considerable disagreement in classifying calcium severity between individual raters when using formal scoring systems. Further agreement and reliability studies are therefore required to confirm whether the disappointing agreement and reliability results found in the current study accurately reflect the performance of these scoring systems.

5.4.3 Additional aspects of grading of severity

As described above, simplification of the scoring systems into two grades of “mild’ and “severe” was necessary to allow comparison of grading between systems. The criterion of bilateral calcification to differentiate between mid and severe grades of calcium was chosen based on the validation studies that suggest that bilateral (or 3-4 quadrants on CTA) calcification is the most clinically relevant threshold(182, 184, 209, 283). Guidance on which grades constitute severe calcification is unclear for some of the scoring systems. The PACSS and Fanelli system use numerical grading rather than descriptive terms and so provide no specific guidance on which grades are considered to be severe. Even when a descriptive nomenclature is used this can be confusing as in the case of the PARC system that designates the grades with bilateral calcium as ‘moderate’ and “severe” but is based, without change to the grading criteria, on the system used in the COMPLIANCE 360 study that used the terms “moderate/severe” and “severe” for these grades (168).

The Fanelli system was found to allocate a smaller number of cases to the severe category than the DEFINITIVE Ca++/PACSS/PARC systems. It is possible that the Fanelli system may have allocated the severity of cases more appropriately given that it was the only method to find a significant difference in IVUS measurements between mild and severe grades.

Up to now, validation of calcium scoring against clinical outcomes has been primarily performed for angiographic soring systems(182, 209). The only validation data that incorporates CTA imaging is from Fanelli’s original paper(184) and that study had some recognised limitations including relatively small sample size and lack of analysis of potential confounding variables(284). The results of the current study suggest that it would be valuable to include CTA imaging into future calcium scoring validation studies and include the Fanelli scoring system, along with traditional angiographic scoring, to enable assessment of the relative performance of a fuller range of scoring

systems. Including IVUS in future studies would also be useful as it provides an accurate referece standard for

A limitation of all the current calcium scoring systems is that it remains unclear what constitutes a clinically significant degree of calcium and it may be that the current criteria may not represent the optimal methods for identifying clinically important calcification(274). There are currently few large studies providing validation of current methods(209) and further validation studies are required to provide better data to ensure that optimal methods are used for assessing calcification in future studies and guiding clinical practice. The poor performance of angiography at characterising calcium suggests that the addition of IVUS and CTA in such projects would add value by more precisely defining the actual calcium present.

5.4.3.1 Limitations

The current study was limited by its small sample size; however this was the largest sample that could be analysed within the constraint of the availability of the surgeons to act as raters for this study. The analysis of the Fanelli system was hampered by a reduction in sample size due to some cases not having prior CTA scan or having CTA scans performed more than six months prior to the procedure. Despite this, the sample size reported here represents the largest to date using IVUS data to assess the performance of calcium scoring systems.

In most cases the imaging used to assess calcium severity was single-plane angiography. It is possible that imaging in orthogonal planes may have produced different results, particularly for assessment of unilateral vs. bilateral calcification as this is a parameter that is likely to be affected by the relationship between the direction of the imaging plane and the distribution of calcium around the wall. A study comparing single and orthogonal plane imaging with IVUS findings would be useful for clarification. Single versus orthogonal imaging may also have an effect on inter-rater reliability and this also warrants further investigation. Interestingly, none of the scoring systems investigated in this study specify whether single or orthogonal imaging planes should be used, although the COMPLIANCE 360 study, which the PARC system is based, used orthogonal angiography. Give the fair to moderate agreement and reliability results found in the current study it may be prudent to routinely employ orthogonal imaging when assessing calcium severity, however the increased contrast dose and radiation (particularly to the operator) should also be considered. A comparative study as suggested above could also help to clarify this issue by defining the potential benefit in accuracy and reliability that might be gained against the potential risks.

The imaging is this study was not core lab adjudicated, however the analysis of the angiographic imaging reported were independently performed by trained interventionists blinded to clinical presentation, procedural information and clinical results. It could be argued that the use of

interventionists with standard training rather than core lab personnel is also a potential strength of the current study as it may provide results that are more generalizable to the performance of calcium grading in the general clinical practice than those from a core lab with staff who are specialised in image analysis.

This analysis was limited to four scoring systems and other systems could have been included. The three angiographic systems investigated in the current study were chosen because they represented the range criteria that are commonly applied and also because they had been the subject of previous comparative studies by other investigators(182, 210). The Fanelli system was chosen as it was the only example available using a different form of assessment. The type of calcification (e.g. intimal v medial) was not reported because most systems do not use this as a classification criterion.

This was not a validation study and this study was not designed to address the question of what degree of calcium severity is the best predictor of poor outcome.

5.5 Summary

All the calcium scoring systems tested tended to allocate more severely calcified lesions into higher grades of severity; however, there was considerable variability in results within grades for all systems. The simplified Fanelli system was the only system with a significant difference in lesion parameters between mild and severe grades. The angiographic-based DEFINITIVE Ca++, PACSS and PARC scoring systems were identical at grading cases when simplified into comparable scales. There was moderate difference in agreement and reliability between these systems and the hybrid angiography/CTA Fanelli system. Inter-rater agreement and reliability were fair to moderate for all of scoring systems with sizable differences in allocation of cases between raters observed.

Ideally, future validation studies of calcium scoring systems should include IVUS imaging to provide additional anatomical information about the performance of these scoring systems in allocating calcium severity. The inter-rater reliability reported in the current study was low. There are no previous studies available for comparison and further investigations are required regarding inter-rater variability due to the lack of current data. The inclusion of CTA imaging should also be considered as the results of this study suggest that using CTA to grade calcium severity may confer some benefits.

6 A COMPARISON OF ANGIOGRAPHIC DISSECTION CLASSIFICATION SYSTEMS USING IVUS IMAGING

6.1 Introduction and aims

Dissection is a common finding after peripheral endovascular intervention(211). Severe dissection is associated with poorer outcomes whilst mild dissection does not appear to have the same risk (18-20). The consequences of dissection therefore vary depending on severity, with mild dissection not requiring further treatment but severe dissection usually requiring further treatment, usually in the form of adjunctive stenting to ensure an adequate lumen(40, 214).

Reliable differentiation between mild and severe dissection is critical to decision-making in relation to whether further treatment is required. The decision to treat or not has consequences as the placing of a stent creates the risk of LLL due to the development of ISR(203, 215) while leaving a severe dissection untreated increases the risk of earlier loss of patency due to an inadequate post-treatment lumen and associated low blood flow(179). Failing to correctly differentiate the severity of dissection therefore has implications for both over and under treatment.

Grading of severity dissection is subjective and is usually based on visual assessment of lumen reduction and evidence of flow-limitation. Grading systems have been created to categorise dissections according to severity. There are two currently available dissection grading systems that have been used in the peripheral arteries: the National Heart Lung and Blood Institute (NHLBI) classification(224) and the Kobayashi classification(19).

The NHLBI classification was developed for use in the coronary arteries with evidence supporting its use in these arteries(218, 224-226, 285, 286). It has also been used in the peripheral arteries with validation data available confirming that severe categories of dissection have an increased risk of poor anatomical or clinical outcome(20, 179). Moderate to good agreement between observers has been reported in the coronary arteries(226). There is no data available for reliability of NHLBI classification in the peripheral arteries.

The Kobayashi classification is a more recent system designed specifically for the peripheral arteries(19). Validation data was provided in the original report of this classification system. Reliability testing was also reported in this study with excellent inter-rater agreement.

The two available classification systems have different designs, with the NHLBI method offering six grades of severity based on patterns of appearances and the Kobayashi system having only two grades of severity based on solely on the proportion of the residual lumen diameter occupied by the dissection. Given these differences it is possible that the two systems may categorise dissection severity differently. If this is the case there is the potential for inconsistency in the reporting of dissection in clinical trials depending on which system is used. There have been no comparative studies investigating either the degree of agreement or the reliability between the two classifications. It is not clear if there are any significant differences between how the two classifications perform at grading dissection and a better understanding of the relative performance of each system would assist with moving toward a standardised system.

IVUS is able measure a range of quantitative parameters to assess dissection severity and has been shown to have higher sensitivity for detection of dissection than angioplasty(10). IVUS therefore provides a quantitative method for assessing the severity of dissections and so can be used to assess how well classification systems perform at categorising severity of dissection.

Given the differences in classification criteria and design complexity it is possible that there may be differences in reliability between the classifications. Inter-rater reliability has not been assessed for the NHLBI system in the in the peripheral arteries and reliability has not been tested for both systems in the same sample. The Kobayashi system is simpler in design than the NHLBI classification and therefore might be expected to have better inter-rater agreement.

This study was undertaken to investigate how well the NHLBI and Kobayashi dissection classifications agree at classifying dissection severity, and to compare the reliability of the two systems.

6.1.1 Study aims

The aims of this study were to investigate how well the NHLBI and Kobayashi classifications agree in categorising severe and mild dissection, and to compare the inter-rater reliability of the two classifications, using IVUS as the gold standard test for assessment of the angiographic appearances.

6.1.2 Research questions

This chapter will present and discuss the findings from research performed to answer the following research questions related to the aims stated in section 6.1.1.

Research question 3 (RQ3): are there significant differences in IVUS anatomical parameters for severe dissection between the NHLBI and Kobayashi systems and are there differences in inter-rater reliability between the systems?

6.1.3 Hypothesis

The hypotheses related to the aims and research questions were:

Hypothesis 3: There will be a significant difference in IVUS dissection parameters between the NHLBI and Kobayashi classification systems for severe dissection, and inter-rater reliability will be higher for the Kobayashi classification than for the NHLBI classification.

6.2 Methods

6.2.1 Study sample selection

A sample of 60 consecutive patients was obtained from the IVUS RCT database. The inclusion and exclusion criteria for subjects enrolled in the IVUS RCT are detailed in Chapter 3 of this thesis.

6.2.2 Angiographic analysis and dissection grading

Two vascular surgeons, regularly performing peripheral endovascular interventions, assessed the cases for the presence of dissection. They were blinded to the patient data, clinical presentation, procedural information and the outcomes of the procedures. They were provided with instructions on how to grade dissections for both the NHLBI and Kobayashi classification systems and a scoring sheet for entering the required information. Each rater had a one-on-one training session with the candidate on the scoring criteria for the NHLBI and Kobayashi classification systems and method of recording scoring data. They then performed ten trial cases followed by a review session with the candidate to check that dissection classification and data entry was being performed as per the study design. Once this had been confirmed, scoring of the 60 cases was able to commence.

Images from the angiographic procedures were viewed on the hospital PACS system (Vue RIS v11.0.14.35, Carestream Health, Rochester, New York). The PACS system holds different types of image files in different folders and the raters were asked to open the folder holding angiographic images. They were instructed not to access the folders containing the radiology report, request form and pictorial worksheet, to ensure they remained blinded to case details. The raters were required to identify any dissections seen and grade each dissection according to NHLBI and Kobayashi dissection classification systems.

The NHLBI classification provides the option of six grades of dissection, increasing in severity from Type A to Type F. These were originally created for use in the coronary arteries (218, 224, 285, 286) and were slightly modified for use in the peripheral arteries were proposed by Fujihara et al.(20). These modifications were limited to simplification of the grade descriptions without substantive changes. Peripheral artery validation of the NHLBI classification using these modified criteria has been reported by Fujihara et al.(20), and these were the criteria that were used for image assessment in the current study (Table 6.1). There is no grade in the NHLBI classification for a vessel with no dissection and therefore an extra grade was added to the scoring sheet to allow for

recording of no dissection.

Table 6.1 NHLBI dissection classification used for the current study, adapted by Fujihara et al. (4)

Dissection grade	Criteria
	No dissection seen
Type A	Dissection with minor radiolucent areas
Type B	Linear dissection
Type C	Dissection with contrast outside the lumen
Type D	Spiral dissection
Type E	Dissection with persistent filling defect
Type F	Dissection with total occlusion without distal antegrade flow

The Kobayashi system was designed specifically for use in the peripheral arteries and was applied in the current study as designed, without modification. This system provides a grade for no dissection and the criteria for the three available grades are presented in Table 6.2.

Table 6.2 Kobayashi dissection classification

Grade	
A	No angiographic dissection
B	Mild dissection: width of dissection less than one third of the lumen
C	Severe dissection: width of dissection more than one third of the lumen

Examples angiographic images of dissection grades in the peripheral arteries for the NHLBI classification have been previously published by Fujihara et al (20), (Figure 6.2). Example angiographic images were produced for the Kobayashi classification by the original authors (Figure 6.2) (19). These images were provided to the raters to assist with interpretation of the angiographic images.

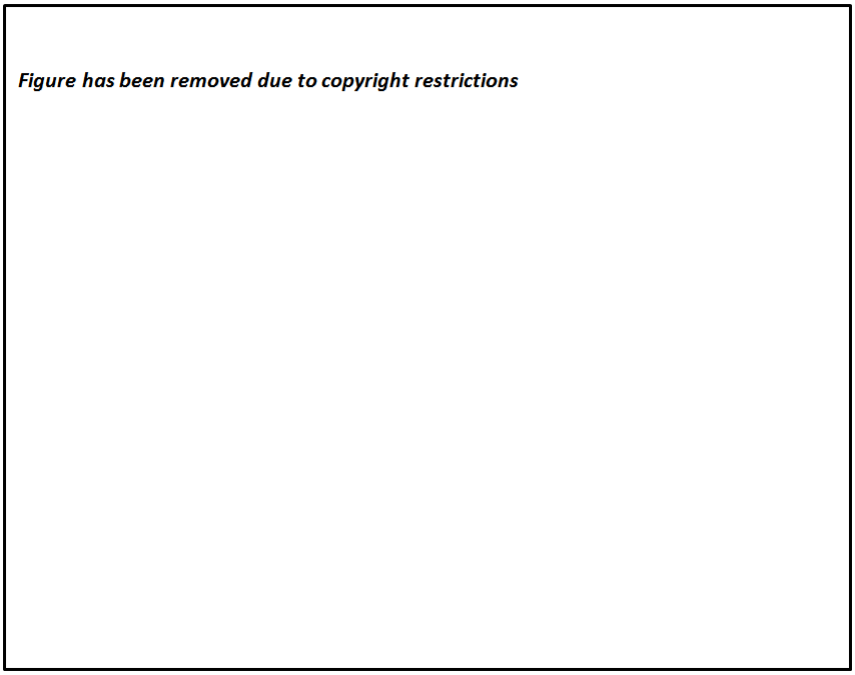

Figure 6.1 Example images of dissection patterns according to the NHLBI classification system, from Fujihara M. et al.(4)

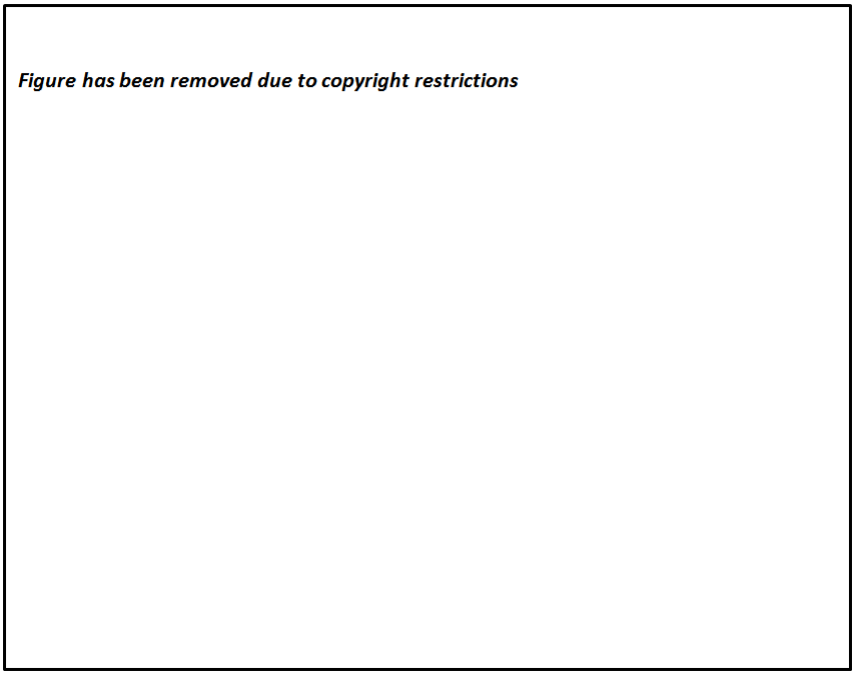

Figure 6.2 Example images of dissection patterns according to the Kobayashi classification, from Kobayashi et al. (3)

The results for each case from each rater were then entered into a database to allow comparison of results. An overall score, for each classification system, was required in each case to allow comparison between the dissection classification and with the IVUS findings for each case. In cases where the two scores agreed this then became the final score for that particular case and was entered on to the study database. When the two scores were different a consensus process was used to reach agreement. For the census process a third rater, trained in the method as described above and blinded to the results of the original two raters, assessed the images in which there was disagreement and produced a third score. If two out of three scores agreed, this became the final score and was entered onto the database. If all three scores were different a consensus meeting was held to reach a final score.

Because the NHLBI has more potential grades available than the Kobayashi classifications it was necessary to condense these into a simplified scale of three grades to allow comparison of agreement and reliability between the two classifications. A simplified NHLBI score was generated for each case by grouping scores into three grades that matched the Kobayashi grades. The grades created were no dissection, mild dissection (Type A and B) and severe dissection (Type C-F). Although the NHLBI classification does not explicitly define which grades are considered severe, the threshold between mild and severe dissection was set between Type B and C dissections because this is the most common way that this classification has been interpreted in validation of this classification(18, 287) and clinical trials(2, 179, 180).

The classifications were further simplified by dichotomisation of scores for each system into severe or non-severe categories by combining mild and no dissections into one group to allow creation of a 2x2 contingency table and the generation of measures of agreement. No dissection and mild dissection were grouped together because they have the same significance in relation to further treatment, i.e. for both of these results no further treatment would be indicated whereas severe dissections may require further treatment.

6.2.3 IVUS assessment of dissection

IVUS cases were analysed by the candidate, blinded to the results of the angiographic grading by the vascular surgeon raters, using IVUS review software (echoPlaque 4.3, INDEC Medical Systems, Los Altos CA). In each case, the post-treatment IVUS pullback was reviewed and any segments with dissection were identified. The pullback rate for each case, expressed as frames/mm, was calculated by dividing the total number of frames in the pullback (minus any frames when the catheter pullback was stationary) by

the distance of the pullback measured in mm. The frame numbers for the proximal and distal extent of the dissection were recorded and the length of the dissection was estimated by dividing the number of frames involving the dissection by the frame rate. The frame containing the maximum degree of dissection was identified and dissection parameters were obtained from this image.

Quantitative parameters related to the dissection for each case were obtained using the measurement tools of the IVUS review software and were entered into the study database.

IVUS dissection parameters included:

- Dissection length (mm), defined as the maximum longitudinal length the of the artery with consecutive IVUS frames containing evidence of dissection
- Maximum dissection arc (degrees), defined as the central angle of an arc from the free tip of the dissection to the point where the dissection flap met the vessel wall (Figure 6.3), with the centre of the arc being the centre of the lumen (definition adapted from consensus guidelines for arc of calcium measurement (25))
- True lumen area (mm^2), the lumen area corresponding to original pre-dilation lumen, defined as the lumen area bounded by the intima and the inner surface of the dissection flap (Figure 6.4), measured at the level of maximum dissection stenosis
- Dissection lumen area (mm^2), the lumen area between the dissection and the vessel wall, defined as the lumen area bounded by outer surface of the dissection flap and the vessel wall (Figure 6.54), measured at the level of maximum dissection stenosis
- Dissection flap area (mm^2), the area of atheroma dissected off the wall into the lumen. Defined as the area bounded by the vessel wall and the free edges of the dissection, measured at the level of maximum dissection stenosis. Measurement was only be performed if the dissected plaque was a discrete entity without extension around the vessel wall (see Figure 6.5 A and B) for examples of a dissection flap suitable for measurement and a dissection flap not suitable for measurement)
- Percentage residual area stenosis, calculated by the equation: residual area stenosis= (true lumen area/reference vessel lumen area) x100 (25)
- Percentage residual diameter stenosis, calculated by the equation: residual diameter stenosis=(true lumen diameter/reference vessel lumen diameter) x100

- Reference vessel area (mm^2), measured in the most adjacent normal segment of the treated vessel immediately proximal to the dissection

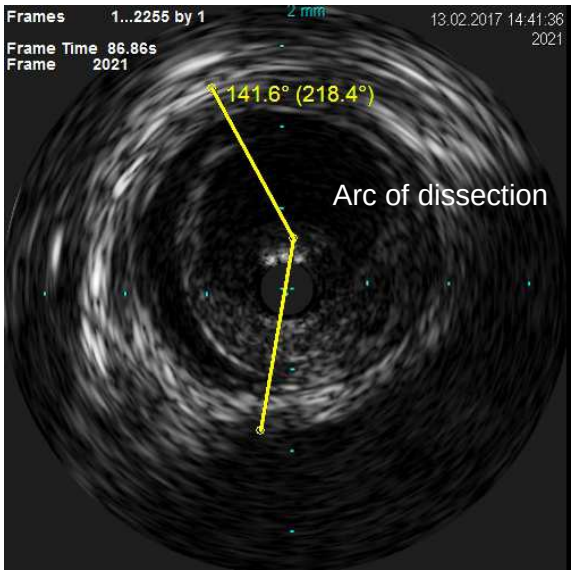

Figure 6.3 Example IVUS image of measurement method for dissection arc with a 141° arc of dissection present

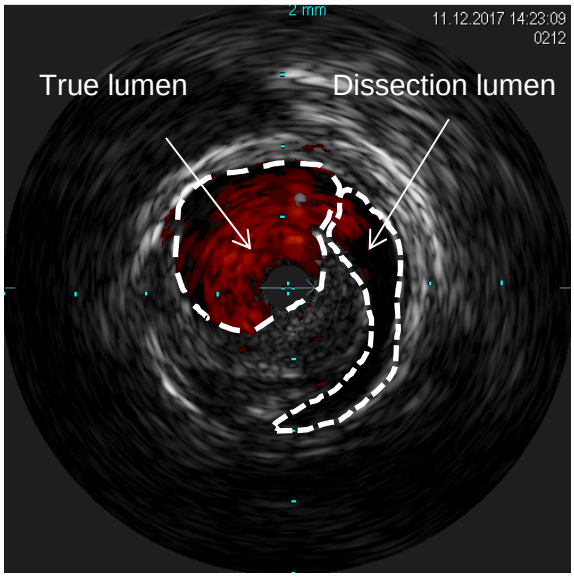

Figure 6.4 Example IVUS image of the true lumen and dissection lumen areas (dashed lines indicate extent of each lumen)

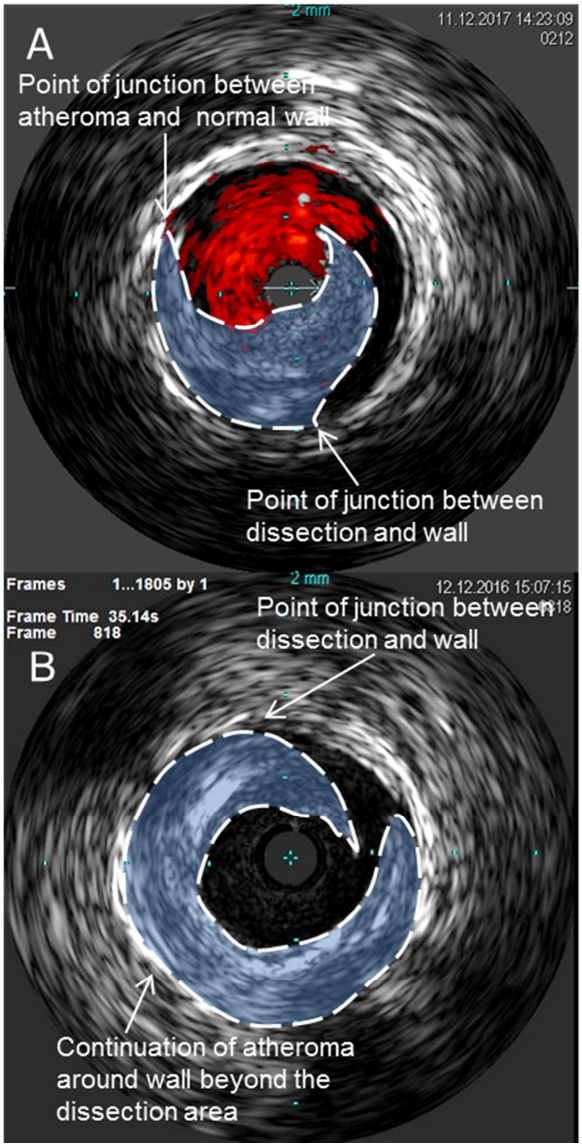

Figure 6.5 A: Example image of dissection flap with discrete margins allowing dissection flap measurement to be performed and B: example image of dissection flap with atheroma extending around most of vessel wall resulting in the dissection flap area measurement not being performed (dashed and shaded area indicates atheroma)

The IVUS parameters were entered into a spreadsheet to enable analsyis with the angiographic data. IVUS dissection parameters were calculated for each grade of dissection severity as defined by each angiographic dissection classifications to allow investgation of anatomical differences between different grades of dissections severity.

Reliability testing was performed by comparing the dissection scores from the two raters for each dissection classification system. Agreement was tested between the two classifications and between raters was performed using the dichotomised classifications to enable measures of specific agreement to be generated.

6.2.4 Statistical analysis

Continuous data was reported as mean (SD) or median (IQR) depending on whether the distribution approximated normality. Categorical data was presented as n (%).Normality of distribution was assessed visually and by the use of Shapiro-Wilks tests of normality. Testing for difference between groups for continuous data was performed using the independent sample t-test or the Mann-Whitney U test depending on whether the distribution approximated normality. Testing of difference of continuous data between more than two groups was performed using ANOVA or the Kruskal Wallis test depending on whether the distribution approximated normality, with post hoc analysis to identify the difference between specific groups using Dunn's pairwise test (adjusted using the Bonferroni method)(276). Testing of difference between groups for categorical data was performed using the chi-square test or Fisher's exact test (for dichotomous variables when a result of ≤5 was expected).

Testing of diagnostic test accuracy was performed using 2x2 contingency tables and calculation of sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios and overall accuracy statistics (288, 289).

Testing of agreement for categorical data was performed by calculating the observed agreement, the positive agreement (also termed specific agreement of a positive rating) and the negative agreement (also termed specific agreement of a negative rating). These were calculated from 2x2 contingency table using the following equations: observed agreement = (a + d)/N, positive agreement (specific agreement on positive rating) = 2a/(2a+b+c), negative agreement (specific agreement on negative rating) = 2d/(2d+b+c) (277, 278).

Testing of reliability of categorical data was performed using Cohen's Kappa (κ) statistic, using unweighted κ for dichotomous data and linear weighted κ for ordinal data with more than two categories(279-282). Interpretation of the level of agreement for Kappa values were based on the recommendations of Mandrekar(279), with the following categories: <0.40 poor, 0.41-0.75 fair to good, and >0.75 excellent agreement.

6.3 Results

6.3.1 Patient, lesion and treatment characteristics of the sample population

Dissection scoring was performed on 60 patients. The subject demographics, lesion characteristics and treatment data are presented in Table 6.3.

Table 6.3 Patient, lesion and treatment characteristics of sample population

Patient, lesion and treatment characteristics	n=60
Mean age, years (SD)	74.5 (9.5)
Gender - male	
Mean BMI, kg/m^2 (SD)	29.8 (4.9)
Smoking status	
Never smoked	14 (23.3%)
Current or previous smoker	46 (76.7%)
DM	21 (35.0%)
IHD	23 (38.3%)
HT	52 (86.7%)
Hyperlipidaemia	44 (73.3%)
Renal insufficiency (<60ml/min) (SD)	34 (56.7%)
Rutherford classification 3	36 (60.0%)
Rutherford classification 4&5	24 (40.0%)
TASC 1&2	33 (55.0%)
TASC 3	27 (45.0%)
Lesion location	
SFA	23 (38.3%)
SFA/Popliteal	26 (43.3%)
Popliteal	11 (18.4%)
Lesion type	
Stenosis	33 (55.0%)
Occlusion	18 (30.0%)
Restenosis	9 (15%)
Severe calcification (PACSS score 3 or 4)	27 (45.0%)
Median treatment length, mm (IQR)	150 (217.5)
Treatment type	
POBA	2 (3.3%)
DCB	26 (43.3%)
POBA or DCB + adjunctive stenting	4 6.7%)
Primary BMS	2 (3.3%)
Covered stent	5 (8.4%)
Atherectomy/DCB	16 (26.7%)
Atherectomy/DCB + adjunctive stenting	5 (8.3%)

6.3.2 IVUS dissection parameters in relation to severity grading using angiographic dissection classifications

Post-treatment angiography was available for all 60 patients in the sample group. IVUS imaging was performed on 51 patients. IVUS was not available in nine patients, due to

post-treatment imaging not being attempted on seven patients and inadequate image quality due to technical faults in another two patients. Angiography was able to identify 37 of 47 cases of dissection confirmed by IVUS (78.7%) and had a sensitivity of 78.2% (95% CI: 81.1%-97.8%), specificity of 75% (95% CI: 64.3%-89.3%), PPV of 97.2% (95% CI: 97.1%-99.5%) and NPV of 23.1 (95% CI: 12.0%-39.8%) when IVUS was used as the reference standard. There were 10 false negative cases with angiography, i.e. cases where no dissection was seen on angiography but dissection was confirmed on IVUS. There was one false positive case, with a dissection identified on angiography that was not seen on IVUS. This was graded as a Type A dissection by the NHLBI classification and may be due to severe calcification at the treatment site obscuring visualisation with IVUS.

Results for dissection flap area are not included in any of the analysis of IVUS derived parameters presented here because this measurement was only available in 19 of the 47 cases with IVUS dissection data. In the other 28 cases this measurement could not be obtained due to inability to confidently differentiate the dissection plaque from plaque not involved with the dissection.

IVUS dissection parameters for each grading category for the NHLBI classification system are presented in Table 6.4. There was a significant difference between the mean ranks of at least one pair of groups for all IVUS parameters except reference vessel lumen. Results of post-hoc Dunn tests (Bonferroni adjustment) found that all significant differences were between pairs of grades involving the “no dissection” category. There were no differences in any pairs when both categories involved dissection. The number of cases in each grade was small with only the “no dissection” and Type B categories having more than 10 cases.

Table 6.4 IVUS dissection parameters for NHLBI dissection grades (for 51 patients with IVUS imaging available)

	NHLBI classification						
IVUS parameters	No dissection n=14	A n=5	B n=19	C n=7	D n=3	E n=3	p*
Dissection length, mm	5 (16)	23 (77)	26 (47)	56.0 (46)	101	57.0	0.025
Dissection arc, °	52 (85)	65 (94)	99 (57)	92 (42)	102	211	0.019
True lumen area, mm^2	22.3 (9.7)	9.2 (10.9)	10.5 (6.5)	10.1 (15.2)	8.8	9.3	0.003
Dissection lumen area, mm^2	1.9 (2.7)	1.7 (5.6)	4.3 (4.4)	4.0 (3.8)	5.2	5.8	0.016
Residual diameter stenosis, %	17.6 (12.0)	35.6 (26.0)	33.8 (20.0)	24.6 (24.0)	36.0	33.8	0.034
Residual area stenosis, %	25.3 (24.0)	58.9 (39.0)	56.2 (29.0)	43.2 (32.0)	59.0	56.1	0.002
Reference vessel lumen area, mm^2	27.7 (15.8)	21.0 (7.6)	21.7 (11.5)	23.0 (11.8)	21.5	23.4	0.435

All results median (interquartile range), IQR not calculated for samples size <4, *Kruskal Wallis test, there were no cases with NHLBI Type F dissection

IVUS dissection parameters for simplified NHLBI classification system (with grades grouped into three categories of no dissection, mild dissection and severe dissection) and the Kobayashi classification system are presented in Table 6.5. There was a significant difference between the mean ranks of at least one pair of groups for the Kobayashi classification for all IVUS parameters except reference vessel lumen.

Results of post-hoc Dunn tests (Bonferroni adjustment) found that all significant differences were between pairs of grades involving the “no dissection” (for the NHLBI system) or Grade A (for the Kobayashi system) categories. There were no differences in between mild and severe grades of dissection with either system.

Testing of difference for IVUS parameters between the NHLBI and Kobayashi classifications for severe grade dissections found not difference (Mann-Whitney U test: dissection length p=0.896, dissection arc p=0.471, true lumen area p=0.744, dissection lumen p=0.948, residual diameter stenosis p=0.845, residual area stenosis p=0.845 and reference vessel area p=0.794). There was also no difference between the two classifications for the mild and no dissection grades.

Table 6.5 IVUS dissection parameters for simplified (three grade) NHLBI and Kobayashi dissection grades (for 51 patients with IVUS imaging available)

	Simplified NHLBI classification				Kobayashi classification			
IVUS parameters	No dissection n=14	Mild (A&B) n=24	Severe (C,D,E) n=13	p*	A (no dissection) n=14	B (mild dissection) n=28	C (severe disssection n=9	p*
Dissection length, mm	5 (16)	25 (48)	57 (55)	<0.000	5 (16)	32 (48)	52 (85)	0.001
Dissection arc, °	52 (85)	99 (55)	102 (52)	0.019	52 (85)	97 (53)	112 (83)	0.008
True lumen area, mm^2	22.3 (9.7)	10.0 (6.6)	9.9 (7.9)	<0.001	22.3 (9.7)	9.8 (7.0)	9.9 (7.5)	<0.001
Dissection lumen area, mm^2	1.9 (2.7)	3.9 (4.9)	5.3 (3.0)	0.005	1.9 (2.7)	4.2 (4.8)	5.3 (3.0)	0.005
Residual diameter stenosis, %	17.6 (12.0)	33.1 (21)	33.8 (16)	0.004	17.6 (12)	34.1 (20)	33.8 (10)	0.005
Residual area stenosis, %	25.3 (24.0)	56.5 (30)	56.1 (22)	<0.000	25.3 (24)	56.5 (65)	56.1 (14)	<0.001
Reference vessel lumen area, mm^2	27.7 (15.8)	21.7 (11.5)	23.0 (10.5)	0.125	27.7 (15.8)	21.7 (11.1)	23.0 (15.1)	0.103

All results median (interquartile range), *Kruskal Wallis test

6.3.3 Agreement and reliability of dissection grading between NHLBI and Kobayashi dissection classifications

Agreement and reliability testing was performed on all 60 patients in the sample population. Agreement results for the simplified NHLBI and for the Kobayashi classification are presented in Table 6.6. The two systems agreed on severity grading in 56 of 60, giving an observed agreement of 0.93. The reliability of grading between the two systems was κ=0.909 (95% CI:0.823-0.995).

Table 6.6 Dissection scores for simplified NHLBI dissection classification and Kobayashi dissection classification

		Kobayashi classification			
		Severe dissection (Grade C)	Mild dissection (Grade B)	No dissection (Grade A)	Total
Simplified NHLBI classification	Severe dissection (Type C,D&E)	11	4	0	15
	Mild dissection (Type A&B)	0	29	0	31
	No dissection (Type 0)	0	0	16	14
	Total	11	34	15	60

Weighted κ=0.909 (95% CI:0.823-0.995).

Dichotomisation of the NHLBI and Kobayashi classifications was performed and the positive agreement was 0.85 and negative agreement was 0.96. Prevalence of severe disease by the NHLBI system was 25.0% and 18.3% by the Kobayashi system.

6.3.4 Inter-rater reliability for NHLBI and Kobayashi dissections classifications

Results for inter-rater testing of agreement and reliability for the NHLBI classification system are presented in Table 6.7. Observed agreement was 0.50 (30 of 60 cases) with a fair reliability of κ=0.469 (95% CI:0.303-0.636). Prevalence of severe dissection (Type C-E) for Rater 1 was 8.3% for Rater 1 and 30% Rater 2.

Table 6.7 NHLBI dissection classification scores for two raters

		NHLBI grade – Rater 2						Total
		None	Type A	Type B	Type C	Type D	Type E	
NHLBI grade - Rater1	None	12	3	3	1	0	0	19
	Type A	1	1	4	1	2	1	10
	Type B	1	2	14	5	3	1	26
	Type C	0	1	0	0	1	0	2
	Type D	0	0	0	0	0	0	0
	Type E	0	0	0	0	0	3	3
Total		14	7	21	7	6	5	60

Weighted κ=0.469 (95% CI:0.303-0.636)

Results for inter-rater testing of agreement and reliability for the Kobayashi classification system are presented in Table 6.8. Observed agreement was 0.68 (41 of 60 cases), with a moderate reliability of κ=0.536 (95% CI: 0.360-0.711). Prevalence of severe dissection (Grade C) was 8.3% for Rater 1 and 30% for Rater 2.

Table 6.8 Kobayashi dissection classification scores for two raters

		Kobayashi grade – Rater 2			Total
		Grade A	Grade B	Grade C	
Kobayashi grade - Rater1	Grade A	12	7	0	19
	Grade B	2	24	7	33
	Grade C	0	3	5	8
Total		14	34	12	60

Weighted κ=0.446, p=0.049

6.4 Discussion

There was no difference in IVUS parameters for severe lesions between the simplified NHLBI and Kobayashi classifications. In fact, for most of the IVUS parameters the median values for severe lesions were the same (see Table 6.6). This was also the case when mild dissections were compared between the classifications. There was also very good agreement at categorising dissection as mild or severe between the two classifications systems. The two classifications agreed in classifying severe cases in all but four cases and had an excellent level of reliability (κ=0.909).

The close agreement between the two classifications systems found in the current study suggests that they perform in a similar way in regard to how they categorise dissection severity. This was the first time that the two classifications have been used to grade dissections in the same populations. This result is interesting because the two systems use quite different methods for classifying dissections and it had been hypothesised that there would be a difference in IVUS parameters between the two classifications. Agreement was not perfect between the two systems, with the NHLBI classification classifying four cases as severe that the Kobayashi system classified as mild. Due to the lack of a gold standard reference test and the lack of difference in IVUS parameters between the two systems it is impossible to judge which of these represents a false positive or negative result.

When IVUS parameters were compared between mild and severe categories within each system there was no significant difference. The only significant differences in IVUS parameters between grades were between the “no dissection” category and various grades of dissection. The absolute IVUS parameters for mild and severe grades were very similar for all of the IVUS parameters except dissection length, which was longer for severe dissections. A limitation of this analysis for the NHLBI system was the low number of cases in some of the dissection categories, particularly Type D and E dissections, however there was still no significant difference in IVUS parameters found when the dissection categories were condensed into simplified grades of mild and severe dissections with larger sample sizes.

It was surprising that the true lumen area and lumen diameter stenosis were not significantly different between grades of severity. This is particularly so for the Kobayashi classification as this method uses the degree of residual stenosis as the fundamental parameter for differentiating between mild and severe disease. Lumen area and stenosis would also be expected to be different between grades of severity for the NHLBI system as the more severe grades in this classification (C-F) all imply a reduced lumen (Figure 6.1).

It has been previously demonstrated that IVUS and angiography disagree in assessment of lumen calibre after treatment(70), particularly when dissection is present(8). The planar nature of

angiography is known to be limiting factor in distinguishing true lumen and dissection lumen and is less accurate than IVUS(8). Interpretation of angiography assumes a circular lumen in cross-section and deviation from this with an irregular or elliptical lumen, as may be seen after dissection, could also contribute to the difference between angiography and IVUS findings. It may be that these factors have contributed to the lack of difference in lumen related parameters found between grades of severity in the current study.

Dissection length for severe dissections according to the NHLBI classification were more than double that of mild dissection and about 60% greater for severe dissections according to the Kobayashi classification. The median lengths of severe dissection in the NHLBI Type D category were four times that of mild dissection and almost double that of other grades of severe dissection. Unfortunately, there were only three cases in this category and the difference in length compared to other grades did not reach statistical significance. Length of dissection is not a specific component of the criteria for Type D dissections, which are defined by a spiral dissection appearance, but it is an implied characteristic of this category as spiral dissections are typically longer than the more focal types of dissection. Repeating this analysis with a larger sample size would be useful to clarify whether dissection length is a significant parameter for identifying severe dissection. Interestingly Kobayashi reported poorer clinical outcomes for dissections seen in longer lesions (>100mm)(19). Although they did not report the length of dissections, and it cannot be assumed that dissections were longer when the lesion was longer, it does raise the possibility that dissection length may be an important variable that deserves further investigation.

The arc of dissection is the most commonly quoted IVUS parameter but no difference was seen between mild and severe dissections for this parameter. It is probably not surprising that no difference was found as, unlike the other parameters, there is no equivalent angiographic measurement with which it can be compared. Lumen, stenosis and length parameters can all be obtained with both IVUS and angiography whereas the arc of dissection requires a cross-sectional imaging method. In addition, it is possible to have an extensive arc of dissection that does not protrude far into the lumen and therefore does not necessarily reduce the lumen area (Figure 6.3).

6.4.1 Inter-rater agreement and reliability

Prior to commencement of this study, it was hypothesised that the Kobayashi classification, due its simplicity of design, would have better inter-rater agreement and reliability than the more complex NHLBI classification. While inter-rater testing did confirm that the Kobayashi system had slightly higher reliability (κ=0.536) compared to the NHLBI system (κ=0.469), there was a large amount of overlap of 95% CIs of the kappa values suggesting that this difference may not be significant. These results are only fair to moderate reliability and the observed agreement (0.50 for the NHLBI system and 0.68 for the Kobayashi system) was also disappointing. These results raise doubts about whether either system has sufficient reliability for clinical use.

It should be noted that there was a systematic difference in ratings between the two raters for both classification, with Rater 2 consistently scoring more dissections as severe. This difference was greater for the NHLBI system (5 severe dissections for Rater 1 and 18 for Rater 2) than for the Kobayashi system (8 severe dissections for Rater1 and 12 for Rater 2). The bias in severe ratings between the two raters in the current study is interesting because these individuals had similar training backgrounds at the same training institutions and so might be expected to reach similar interpretations of these cases. The difference in ratings therefore may be due to inherent differences in perception of dissection severity between individuals rather than a product of training and experience.

The inter-rater reliability results for the current study for the Kobayashi classification (κ=0.536) were worse than those in Kobayashi's original report, where kappa values in excess of 0.9 were reported(19). Although caution should be applied when comparing kappa results between studies, due to it being a relative rather than absolute statistic(279), it seems clear that the classification has performed very differently in the current study compared to Kobayashi's original report. There is no data on inter-rater reliability for the NHLBI system in peripheral arteries to compare with the current study, however a kappa of 0.66 has been reported for NHLBI grading of coronary artery dissections performed by a core laboratory(226). This is higher than that found in the current study (κ=0.469), albeit by a smaller margin than for the Kobayashi classification.

The reason for these differences is unknown although some of the difference in NHLBI results may be related to application in different vessels. The larger size of the femoropopliteal arteries and more extensive nature of disease may result in differences in how dissection appearances are interpreted. The reasons for the difference in reliability between the current study and those reported by Kobayashi are also not clear but may relate to the level of expertise and knowledge of the raters. The Kobayashi raters, as part of the investigation team that created the classification, are likely to have had a more in-depth understanding of the classification system than the raters in the current study and, due to the process of formulating the classification system, have a more consistent interpretation of how to apply the classification criteria. The typical interventionist performing endovascular interventions in everyday clinical practice is unlikely to have this level of expertise or interest and the results from the current study may therefore be a more realistic approximation of the reliability of this classification in clinical practice. A similar phenomenon may also apply to the results of core laboratory adjudication (as used in the report of reliability of the NHLBI classification) where the processes of quality control used in core laboratories would tend to bring adjudicators ratings closer toward agreement. The results of the current study may therefore represent real-world data on how interventionists interpret dissection appearances. If this is the case it suggests that both classification systems are likely to be unreliable in everyday practice.

6.4.1.1 Limitations

Single plane angiography was used in the current study and this may not characterise dissection features as well as orthogonal imaging. The type of angiography is not stipulated in the methods for either classification system. The type of angiography was not defined in the validation studies or in studies that report reliability so it is unclear if this is a reason for the differences in results between the current study and previous studies.

The sample of this study is small and this may have contributed to the lack of difference in IVUS findings between grades of severity. It is possible that with a larger sample size there may have been significant differences in some IVUS parameters between severity grades. The very small differences found between mild and severe grades of dissection for most IVUS parameters (other than dissection length) suggest that an increase in sample size may need to be quite large for a difference to become apparent.

This is not a validation study and so does not address the question of which grades of dissection or IVUS parameter measurements are predictors of poor anatomical or clinical outcome. The RCT from which the patients for the current study were obtained was unlikely to be large enough for a validation study and also may not have been a suitable source due to confounding variables of randomisation into IVUS and non-IVUS groups and heterogeneity of treatment methods.

6.5 Summary

The current study found good agreement between the two classification systems with no difference in IVUS parameters of dissection between them. There was good reliability for detecting severe dissection between the classifications. Inter-rater reliability for each classification system was only fair to moderate and raise concerns that the variability in interpreting dissection with either classification may be higher than acceptable. The reliability reported here was lower than previously reported however caution should be applied when comparing reliability between studies and repeating this testing with a larger sample would be valuable. An additional finding was that neither system was able to differentiate between mild and severe dissection, as defined by IVUS dissection parameters.

These results suggest that the two classification systems are roughly comparable for at allocating the grade of dissections but raise concerns about both the ability of these classifications to accurately define the severity of dissection and the reliability of both classifications. Further investigations are required to confirm these results and should include the use of IVUS imaging to provide anatomical confirmation of the angiographic-based grades.

7 ASSESSMENT OF IVUS IMAGE QUALITY FOR ATHEROMA VOLUME ESTIMATION USING CORE LABORATORY ANALYSIS

7.1 Introduction and aims

IVUS-based estimation of atheroma volume has previously been reported in studies of atherectomy in the peripheral arteries(21, 23) and comparing atheroma burden in the coronary and peripheral arteries(22). Acquisition of accurate atheroma volumes would enable quantitative assessment of the effectiveness of atherectomy. Atheroma burden is known to be an important factor in outcomes of patient with CAD(252, 290, 291) and the ability to obtain atheroma volumes in patients with PAD could assist with improving understanding of the role that atheroma burden plays in PAD.

Studies reporting IVUS-based atheroma volume in the peripheral arteries have used methods developed by core laboratories for the coronary arteries(21-23). These methods were developed for studying atheroma progression/regression in response to anti-atherogenic therapies. It relies on systematic sampling of the IVUS imaging with lumen and vessel areas being obtained throughout the segment under analysis(193, 231). Strict technical criteria are applied to ensure that the IVUS images used are of sufficient quality to allow accurate volume estimation. The imaging conditions of the peripheral and coronary arteries are different with more extensive calcification a feature of the peripheral arteries(17). Calcification is known to limit measurement of vessel area from IVUS(25) and a study comparing MRI and IVUS found that vessel area measurements could not be obtained in almost half of the IVUS images(24). There are no equivalent guidelines for technical quality of IVUS based atheroma volume analysis in the peripheral arteries. The previous studies reporting atheroma volume analysis in the peripheral arteries have not specifically reported on whether calcium had an impact on image quality or analysis accuracy(21-23).

It seems likely, based on the prevalence of calcium in the peripheral arteries, the methodology used for atheroma volume analysis and the limited evidence on how many IVUS images cannot be analysed, that a significant proportion of IVUS images obtained in the femoropopliteal artery will not be technically suitable for measurement. The current study was performed to establish what proportion of IVUS frames were suitable for full analysis using standard core laboratory criteria and how many cases had IVUS imaging that was technically adequate for atheroma volume estimation. This information will help establish whether IVUS is a viable method for whole-of-lesion atheroma estimation in patients with peripheral artery lesions.

7.1.1 Study aims

The aim of this study was to investigate whether IVUS was able to provide technically adequate

imaging for atheroma volume estimation, in a series of patients who underwent IVUS imaging during peripheral arterial endovascular interventional procedures.

7.1.2 Research questions

This chapter will present and discuss the findings of research performed to answer the following research question related to the aim stated in section 7.1.1

Research question 4 (RQ4): How many cases undergoing IVUS during peripheral endovascular intervention had an adequate proportion of suitable images for performing atheroma volume analysis?

7.1.3 Hypothesis

The hypothesis related to the aim and research question was:

Hypothesis 4: Less than half the cases assessed by core laboratory analysis will have an adequate proportion and distribution of frames suitable for atheroma analysis.

7.2 Methods

7.2.1 Study population and IVUS imaging acquisition

IVUS imaging acquisitions of 42 consecutive patients enrolled in the IVUS RCT (reported in Chapters 3 and 4) underwent core laboratory analysis. The patient, clinical and lesion characteristics for each patient were obtained from the IVUS RCT database.

All IVUS examinations were performed with manual pullback of a Volcano Eagle Eye or PV018 20MHz catheter, with pullback performed at a steady rate by the operating surgeon. As described previously in Chapter Two, the pullback was performed under fluoroscopic guidance. The start position, end position and catheter position at 2cm intervals throughout the pullback were recorded for each case. The start and end frames of any pauses in pullback (i.e. when the pullback was stopped to allow re-positioning of the table within the imaging field) were recorded. Fiducial side-branches were also identified to allow confirmation of the ruler based catheter position and confirm matching of the positions for each pullback. The start and end of the treatment zone, relative to the radio-opaque ruler, was recorded during the post-treatment IVUS acquisition. The corresponding start and end frames of the treatment zone on the pre-treatment IVUS pullback were then located by correlation with the post-treatment pullback by the use of the ruler position information and nearby fiduciary branches. This allowed matching of treatment zone from the pre- and post-treatment for comparative analysis.

The core laboratory was provided with the following information for each pullback: trial identification, study date, start of pullback frame number, end of pullback frame number, total pullback length (mm), treatment zone start frame number, treatment zone end frame number, and start and end frame numbers for all pauses.

7.2.2 Core laboratory analysis methods

IVUS analysis was performed by the Atherosclerosis Imaging Core Laboratory (AICL), South Australian Health and Medical Research Institute (SAHMRI), North Terrace, Adelaide, South Australia. Analysis was performed using computerised planimetry software (ImageJ 1.42o, National Institutes of Health, USA, http//rsb.info.gov/ij) customised for IVUS analysis by the Cleveland Clinic, Cleveland OH. The core laboratory was blinded to patient, lesion and procedural information related to each case.

The total pullback length and IVUS image frames (with frames during pauses in pullback excluded) were entered into an automated frame calculation spreadsheet to determine pullback rate for each IVUS pullback. The spreadsheet also auto-entered data into frame calculator fields for both pre and post-treatment time points. This allowed efficient and accurate entry of frame data and output of frame numbers used in the generation of measured stacks for analysis. Any single time point imaging could also be analysed in the same way.

Frames acquired during a pause in catheter pullback were marked as paused and excluded from analysis and not included in the frame rate calculation. A stack of imaging frames through the entire treatment zone was created for each pullback. The frame rate for pullback was calculated for each pullback using the frame calculator, e.g. if a pullback over a distance of 250mm contained 2700 frames, of which 200 frames were acquired during a pause in movement, then the pullback rate was 10 frames/mm (calculated by the equation (2700-200)/250). All pullbacks were analysed in frame increments representing an interval of 2mm, starting from the treatment zone start frame and ending with the treatment zone end frame. In the above example of a 250mm pullback of 2500 frames a 2mm increment represents sampling of every 20th frame. In the above example of a 250mm pullback, if the treatment zone was over a 200mm length then 101 frames at 2mm increments would be analysed. Each stack was generated using a distinct frame calculator because of the potential for different frame rate pullback speeds. The use of 2mm increments, rather than set frame intervals, allowed comparison of roughly matched treatment zones between the pre- and post-treatment pullbacks for each case.

Analysis was performed on the stacked IVUS sample frames within the treatment zone before and after treatment. Quantitative analysis involved manual delineation of the EEM contour (the interface at the border between the media and the adventitia) and the lumen contour (the interface between the lumen and the leading edge of the intima). Each frame was analysed for technical quality to ensure that data gained during analysis was reliable. Frames with technical problems were identified and labelled as inadequate if technical quality limited or prevented measurement from being performed.

EEM contours were not obtained if either of the following image characteristics were present:

- Calcium obscuring an arc of the EEM ≥45°
- Image quality was inadequate to distinguish the contour information of the EEM

Lumen and EEM contours were not obtained if image characteristics matched any of the following categories:

- Side Branch: the vessel wall was distorted by a large side branch.
- Calcium: the vessel contained an excessive amount of calcification (>45° arc of calcium) with associated acoustic shadowing and/or had an irregular intimal surface that prevented both lumen and EEM contour assessment
- Imaging artefacts: including distortion of wall structures due to mid-line artefact (a discontinuity in echoes due to abrupt vessel movement) that made contour tracking inaccurate, the lumen edge could not be clearly defined due to obscuring artefacts (such as ring-down or grating lobes), poor reflection from the interface, or poor quality image quality for any reason making measurement unreliable

- ChromaFlo: the presence of the colour-coded ChromaFlo flow indicator function distorted the imaging or prevented accurate determination of the lumen and/or EEM contour
- Dissection: a dissection was present in the image and distorted the lumen, making contour assessment inaccurate.

Cases that had few or any frames that could be analysed were marked as technically inadequate and were not included for further analysis. Frames in which both the lumen and EEM measurements could be obtained were termed “fully analysable frames” with frames in which only the lumen was available were termed “lumen only frames”.

All core laboratory analysts performing the analysis of the IVUS pullbacks had previously completed training in core laboratory analysis techniques and successfully completed all on-going quality assurance processes within the core laboratory. After initial analysis each pullback was checked by a second analyst for agreement with any disagreement being resolved by a consensus process.

7.2.3 Core laboratory IVUS parameters

The following dimensions were obtained from the EEM and lumen contours:

- EEM cross-sectional area (CSA), mm^2
- EEM circumference, mm
- EEM maximum diameter, mm
- EEM minimum diameter, mm
- Lumen CSA, mm^2
- Lumen circumference mm
- Lumen maximum diameter, mm
- Lumen minimum diameter, mm
- Plaque thickness (distance between EEM and lumen contours) maximum, mm
- Plaque thickness minimum, mm

Semi-quantitative measurement of calcium was performed on all frames. Calcium was identified by an echogenic signal brighter than the adventitia with corresponding acoustic shadowing. A score for the calcification arc was assigned to each analysed image using the following criteria:

- 0: no calcium present
- 1: calcium with total acoustic shadowing 1-90°
- 2: calcium with total acoustic shadowing 91-180°
- 3: calcium with total acoustic shadowing 181-270°

- 4: calcium with total acoustic shadowing 271-360°

7.2.4 Derived parameters

The quantitative parameters generated by the core laboratory were provided to the clinical research team and further parameters were derived from this data. These parameters included:

- Atheroma area: the area bounded by the lumen and EEM borders. As recommended by clinical guidelines (25, 231) this is the area between the intima and the adventitia consisting of atheroma and media and was referred to as the atheroma area (this parameter is also referred to as the media plus plaque area) and is calculated by the equation:
  Atheroma area = EEM area – Lumen area
- Percent atheroma area: This is a measure of atheroma burden for each frame and is the maximum proportion of the vessel area in any frame occupied by atherosclerotic plaque, calculated by the equation:
  Percent atheroma area= [(Atheroma area)/EEM area] x 100
- Percent atheroma volume (PAV): This is a measure of overall atheroma burden and is the proportion of vessel wall volume occupied by atherosclerotic plaque calculated by the equation:
  PAV (%) = [Σ (EEM area – Lumen area)/ Σ EEM area] x 100
- Vessel remodelling index: the EEM area of a frame within the lesion divided by the EEM area at the level of the RVD. Positive remodelling was defined as a remodelling index >1.05 and negative remodelling was defined as a remodelling index of <0.95 (83)
- Plaque eccentricity index: this is a measure of the difference between the maximum plaque thickness (PTmax) and minimum plaque thickness (PTmin). It is calculated using the following equation:
  Eccentricity index= (PTmax - PTmin)/PTmax.
  Eccentric plaque was defined as an eccentricity index ≥0.5 (i.e. plaque with a maximum plaque thickness at least twice the minimum plaque thickness) and concentric plaque was defined as an eccentricity index <0.5 (25).

Calcification parameters derived from the core laboratory data included:

- Segments containing calcium were differentiated between those containing only spotty calcium and those containing calcium lesions
  - Spotty calcification: defined as the presence of small lesions (1 to 4 mm in length) containing < 90° of acoustic shadowing
  - Calcified segments were defined as calcium present for at least 5mm (9, 160)
- Total calcium length: defined as the sum of all calcium lesions, excluding spotty calcium (as defined above), measured in mm

- Maximum segment length of calcium: defined as the longest segment of continuous frames containing calcium, measured in mm

7.2.5 Assessment of technical adequacy of IVUS for quantitative atheroma analysis

There are no criteria for assessing the technical adequacy of IVUS imaging for assessing plaque volume across entire lesions in the peripheral or coronary arteries. Criteria were therefore created specifically for this study. These criteria were based on the assumption that for imaging data to be representative of the lesion as a whole it needed to meet two objective criteria. Firstly, a high percentage of frames needed to be fully analysable (have both lumen and EEM measurements) available and secondly, that these frames needed to be distributed along the entire length of the IVUS pullback.

The percentage of frames available for analysis was calculated for each case by the following equation: (number of fully analysable frames / total number of frames) x 100. The distribution of available frames along each lesion was assessed visually by the use of lesion plots that displayed lumen and EEM area measurements in relation to the lesion length. For these graphs, the lumen area measurements of frames with the lumen area measurement available were displayed in grey and the EEM area measurements for frames with the EEM area measurement available were displayed in black. These were then plotted along the length of each IVUS pullback, with each the data point's position in relationship to the y axis determined by the area measurement and with the position in relationship to the x axis being the sequential order of the sampled frames in the pullback (distal start point at the left and proximal end point at the right). The data points for consecutive analysable frames were joined by lines and gaps between lines therefore represented segments of the lesion where there were no consecutive analysable frames. Each pullback was demarcated into eight equal sub-segments to assist with assessment of distribution of frames along each lesion. To allow easy comparison between cases of the distribution of frames, each pullback was displayed as an equal length along the x axis regardless of the number of frames included. The post-treatment IVUS pullbacks for the cases that had technically adequate pre-treatment IVUS imaging were also assessed for technical adequacy using the same methods.

The thresholds for technical adequacy of an IVUS pullback for atheroma quantification were set as follows: 1) ≥50% of sampled frames must be available for full analysis and 2) uniform distribution of analysable frames along the lesion length, defined as the presence of consecutive analysable sampled frames in all eight sub-segments of the pullback length.

7.2.6 Statistical analysis

Continuous data was reported as mean (SD) or median (IQR) depending on whether the distribution approximated normality. Categorical data was presented as n (%). The use of parametric or non-parametric tests was dependent on whether the distribution of data

approximated normality. Testing for difference between groups for continuous data was performed using independent sample t-test or the Mann-Whitney U test. Testing of difference of paired samples was performed using the paired sample t-test or the Wilcoxon signed-rank test. All statistical analysis was performed using SPSS Statistics for Windows version 24 (IBM Corp, Armonk, NY). The significance level of all testing was set at a p-value of 0.05.

7.3 Results

7.3.1 Patient and lesion characteristics for subgroup with core lab analysis

In four of the 42 cases the IVUS imaging was classified as technically inadequate and these cases were not included in the analysis. The patient and lesion characteristics of the 38 patients with IVUS pullbacks included for analysis are presented in Table 7.1.

Table 7.1 Patient demographics, lesion and treatment characteristics

Patient, lesion and treatment characteristics	n=38
Mean age, years (SD)	74.6 (9.9)
Gender - male	22 (57.9%)
Mean BMI, kg/m^2 (SD)	29.9 (5.6)
Smoking status	
Never smoked	10 (26.3)
Current or previous smoker	28 (73.7%)
DM	13 (34.2)
IHD	15 (39.5%)
HT	32 (84.2)
Hyperlipidaemia	27 (71.1%)
Renal insufficiency (<60ml/min) (SD)	21 (55.3%)
Rutherford classification 3	21 (55.3%)
Rutherford classification 4&5	17 (44.7%)
TASC 1&2	21 (55.3%)
TASC 3	17 (44.7%)
Lesion location	
SFA	16 (42.1%)
SFA/Popliteal	15 (39.5%)
Popliteal	7 (18.4%)
Lesion type	
Stenosis	22 (57.9%)
Occlusion	12 (31.6%)
Restenosis	4 (10.5%)
Severe calcification (PACSS score 3 or 4)	117 (44.7%)
≥50% of lesion length containing calcium on IVUS	22 (57.9%)
Median treatment length, mm (IQR)	150 (195)
Treatment type	
POBA	2 (5.3%)
DCB	22 (57.9%)
BMS	2 (5.3%)
Atherectomy + POBA/DCB	12 (31.5%)

7.3.2 Analysis of pre-treatment IVUS imaging for technical adequacy for atheroma quantification analysis

A total of 4282 sampled frames were available for analysis from 38 cases. Paused frames totalled 643 of the frames acquired and when the paused frames were excluded, a total of 3639 frames remained for core laboratory analysis. The mean number of frames analysed per case was 96,

with a range of 20 to 185.

There were 1431 frames (39.3%) on which no analysis at all could be performed, 1209 “lumen only” frames with lumen measurement only available (33.2%) and 999 “fully analysable” frames in which lumen and EEM measurements were available and were therefore technically adequate for use in volume analysis (27.5%). Complete or partial (i.e. lumen only) restriction in measurement analysis due to image quality therefore occurred in 2640 of 3639 frames (70.5%).

The reasons for frames being technically inadequate for measurement were, in descending order of magnitude: lumen only measured (45.9%), imaging artefact (19.7%), calcium (16.1%), side branch (7.7%), dissection (7.5%) and the use of ChromaFlo function (3.1%).

The proportion of fully analysable frames for each case (both EEM and lumen measurements available) was low, with a median percentage of fully analysable frames per case of 24.6% (IQR= 41.8%). The distribution of cases according to the percentage of fully analysable frames is presented in Figure 7.1 and shows that in only eight cases were ≥50% of frames fully analysable and therefore suitable for use in volume analysis (21.1%).

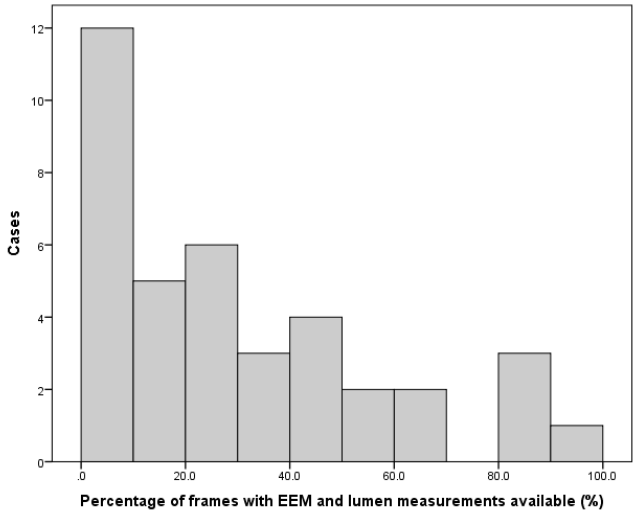

Figure 7.1 Percentage of frames per case with EEM and lumen measurements available for analysis

The distribution of analysable frames along the length of the IVUS pullback did not reach the threshold for technical adequacy (<50% of frames available for full analysis) in for 30 cases and the lesion plots of these cases are presented in Figure 7.2. Visual inspection confirmed that in all of these cases there were at least two sub-segments with no consecutive fully analysable frames indicating that none of these cases met the criterion for uniform distribution along the lesion length. In most cases the results were well below the threshold for technical adequacy with 27 of 30 cases having at least three sub-segments without analysable frames and 25 of 30 cases with fully analysable frames in <40% of all frames. There were only three cases that were close to reaching the threshold for technical adequacy, having 40-49% of frames available for analysis and only two

sub-segments without analysable frames (cases 10, 30 and 33).

There were eight cases with ≥50% of frames available for full analysis and lesion plots of these cases are displayed Figure 7.3. Analysable frames were available in all sub-segments in five of these cases (cases 4, 12, 22, 23 and 25) and these cases constitute the group that were technical adequate for quantitative atheroma analysis, as specified by the technical criteria. The other three cases all had one sub-segment with no fully analysable frames available and so did not meet the technical criteria for adequacy.

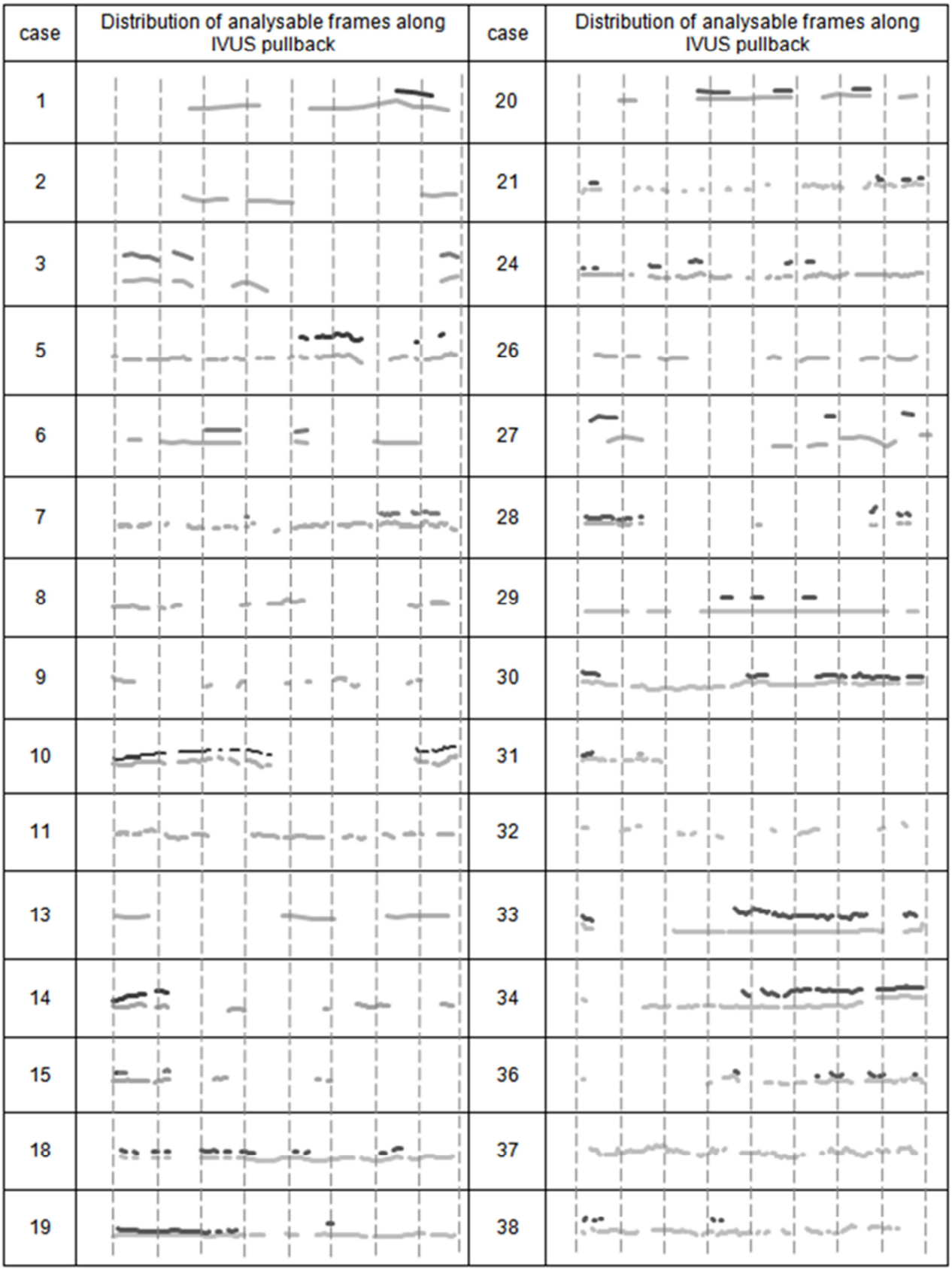

Figure 7.2 Lesion plots of pre-treatment IVUS pullbacks with <50% of frames available for full analysis: frames with lumen and EEM measurements plotted along pullback length. Black lines: EEM area measurement, grey lines: lumen area measurement, dashed lines: length intervals equating to 1/8 of total lesion length

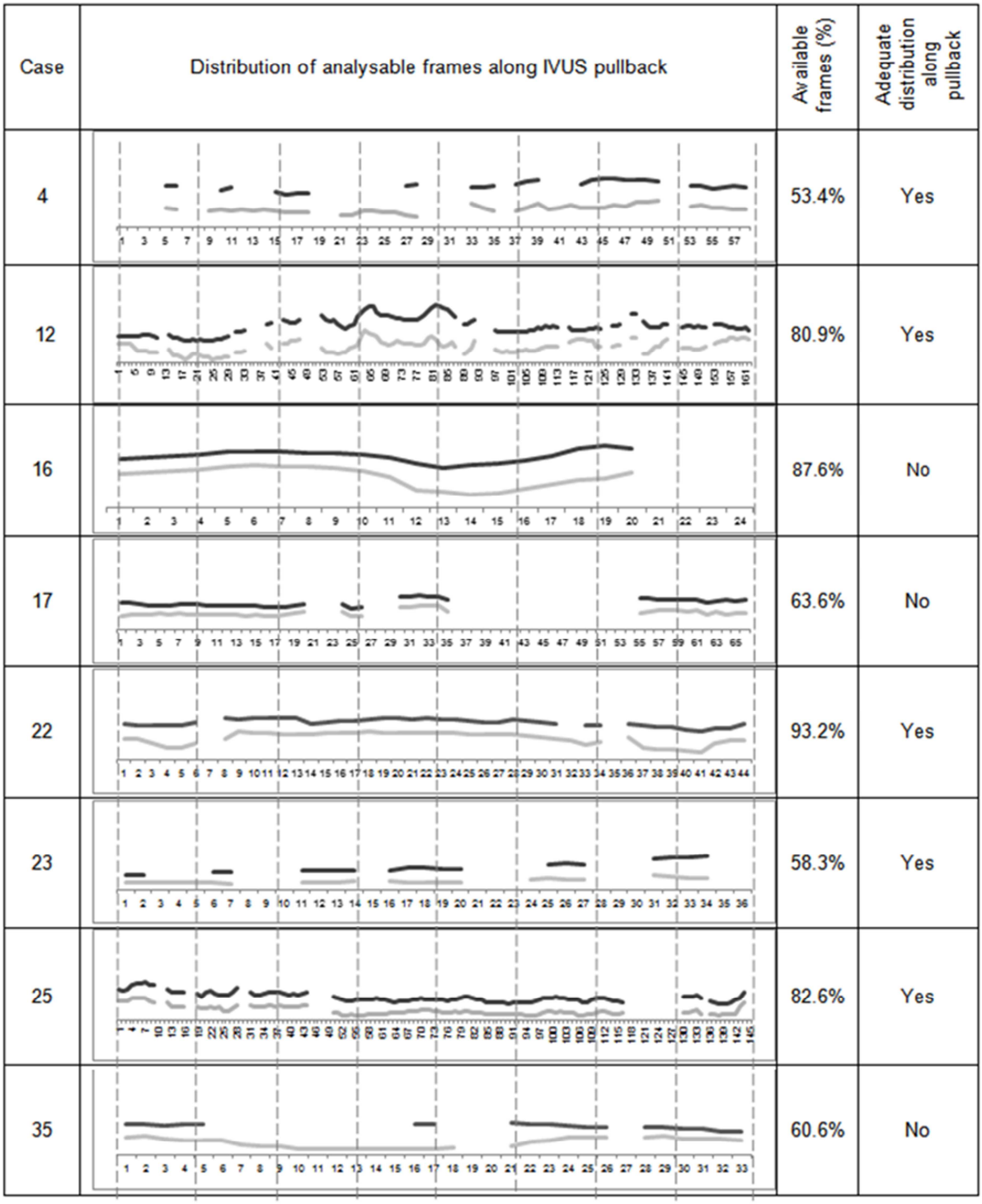

Figure 7.3 Lesion plots of pre-treatment IVUS pullbacks with ≥50% of frames available for full analysis: frames with lumen and EEM measurements plotted along pullback length. Black lines: EEM area measurement, grey lines: lumen area measurement, dashed lines: length intervals equating to 1/8 of total lesion length

Comparison of IVUS vessel and atheroma parameters for cases suitable and unsuitable for analysis is presented in Table 7.2. This found that the proportion of calcium in cases that were technically adequate was significantly less than that for the cases that were not adequate. The mean minimum remodelling index was significantly higher in cases that were not technically

adequate compared to cases that were adequate. There were no other IVUS parameters was no significant different between the two groups.

Table 7.2 Comparison of IVUS vessel and atheroma parameters for technically adequate and technically inadequate cases

	Cases not technically adequate for quantitative atheroma analysis (n=31)	Case technically adequate for quantitative atheroma analysis (n=5)	Significance
Proportion of lesion containing calcium (%), median (IQR)	56.3 (57.3)	4.5 (29.9)	0.040*
Percentage atheroma volume (%), median (IQR)	49.8 (18.5)	56.1 (11.2)	0.282*
Mean atheroma area, mm^2	17.9 (5.5)	17.2 (7.3)	0.797
Mean EEM area, mm^2	35.8 (11.3)	31.8 (12.0)	0.424
Mean lumen area	16.1 (5.9)	14.1 (5.4)	0.445
Mean remodelling index	0.92 (0.13)	0.80 (0.13)	0.051
Mean eccentricity index	0.67 (0.10)	0.71 (0.06)	0.343
Maximum atheroma area, mm^2	23.9 (8.1)	27.9 (16.0)	0.387
Maximum percentage atheroma (%)	63.6 (14.8)	76.8 (6.9)	0.059
MLA (mm^2), median (IQR)	7.7 (6.3)	6.1 (4.6)	0.218*
Minimum remodelling index	0.79 (0.15)	0.59 (0.09)	0.011
Maximum eccentricity index, median (IQR)	0.86 (0.16)	0.93 (0.06)	0.059*

Mean and (SD) and independent samples t-test unless otherwise indicated, * Mann-Whitney U test

7.3.3 Analysis of post-treatment IVUS imaging for atheroma quantification analysis

When analysis was repeated for post-treatment IVUS pullbacks on the five patients with technically adequate pre-treatment IVUS a significant reduction in the percentage of frames that were fully analysable was found compared to the pre-treatment IVUS (median pre-treatment proportion of fully analysable frames=58.3% (IQR=26.1%) vs. median post-treatment proportion of fully analysable frames=26.2% (SD=17.6%), p=0.008, Wilcoxon Signed Rank test) (Figure 7.4).

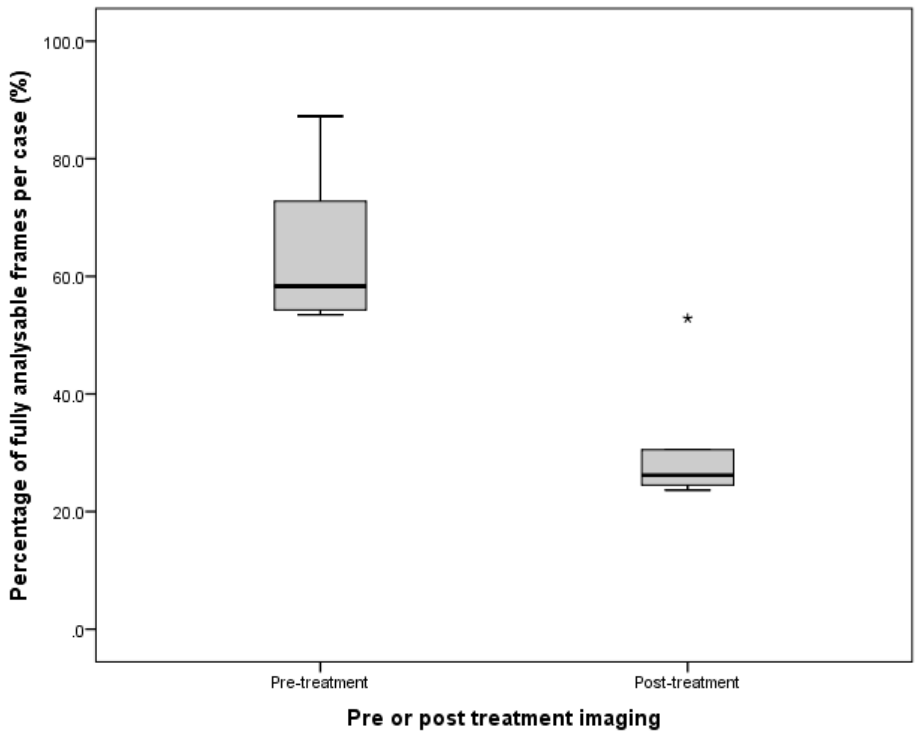

Figure 7.4 Comparison of percentage of fully analysable frames in pre-treatment and post-treatment IVUS for the 5 cases with technically adequate pre-treatment IVUS

There was an increase in number of frames that could not be analysed due to dissection (median frames with dissection per case pre-treatment = 1 (IQR=3) vs. median frames with dissection per case post-treatment = 23 (IQR=57), however this did not reach statistical significance (p=0.080, Wilcoxon Signed Rank test). There was no significant change in the other technical reasons for frames being inadequate for measurement. All five of these cases were treated with plain balloon angioplasty and DCB. Atherectomy was not used in any of these cases.

Lesion plots for the five cases with assessment of post-treatment IVUS revealed that only one case (case 25) had an IVUS pullback that met criteria for technical adequacy for quantitative atheroma analysis, with the other four cases having less than 50% of frames available for analysis and at least two sub-segments without analysable frames (Figure 7.5). Therefore, this was the only case of the initial 38 cases that underwent core laboratory analysis in which both pre- and post-treatment IVUS was technically adequate for quantitative vessel and atheroma volume analysis.

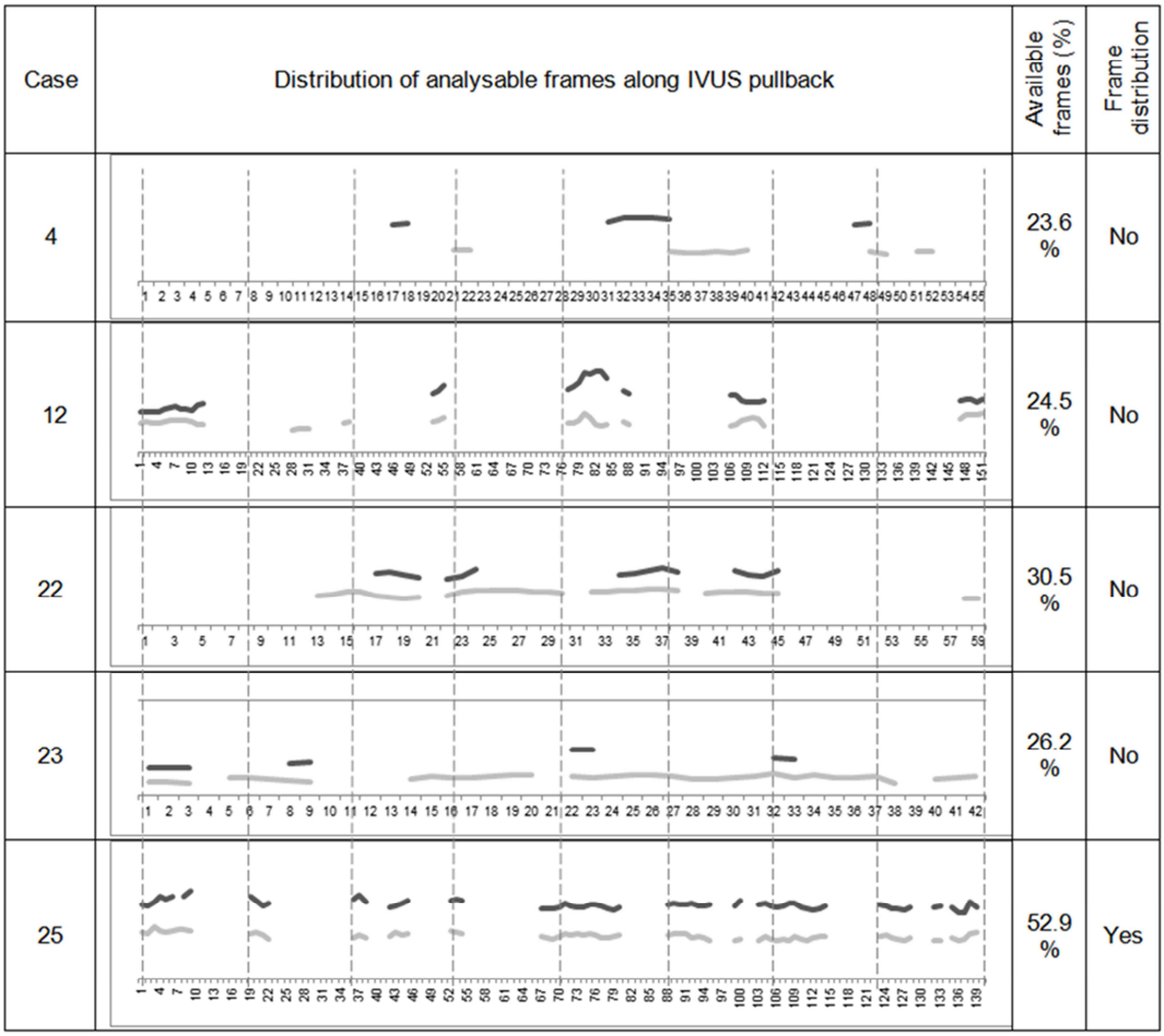

Figure 7.5 Lesion plots of post-treatment IVUS pullbacks of cases with pre-treatment pullbacks that were technically adequate for analysis: frames with lumen and EEM measurements plotted along pullback length. Black lines: EEM area measurement, grey lines: lumen area measurement, dashed lines: length intervals equating to 1/8 of total lesion length

7.3.4 Vessel calcification

Calcium was present in 1739 frames out of the 3639 frames analysed (47.7%). In 236 frames the calcium involved less than 45° of the vessel circumferences and so did not impede analysis, allowing full analysis to be performed. In 1079 frames calcium involved more than 45° of the vessel circumference and EEM measurements could not be obtained and were designated “lumen only” in the analysis. In 424 frames the calcium was severe enough to prevent both lumen and EEM measurements from being obtained. In total calcium was responsible for 1503 frames being excluded from full analysis. This is 56.9% of all the fames that were not fully analysable.

Some form of calcium was seen in all cases. Calcium lesions (length >5mm) were seen in 34 of 38 cases (89.5%), with spotty calcium alone seen in the remaining four cases. The total calcium

length (i.e. the sum of all calcified segments within the lesion, excluding areas of spotty calcium) ranged from 6 to 314mm with a median total length of calcium of 39 mm (IQR=145mm). The distribution of total calcium length per case was markedly skewed with almost two thirds of cases (15 of 26) having a length less than 100mm. The percentage of lesion length containing calcium was more normally distributed with a mean percentage of the lesion length containing calcium of 49.6% (SD=31.3%).

The median length of the longest single calcium segment seen in each case ranged from 6 to 310mm, with a median length of 37mm (IQR: 67mm). The distribution was strongly skewed with more than half having a length of <50mm and over 80% having a length of <100mm (Figure 7.6).

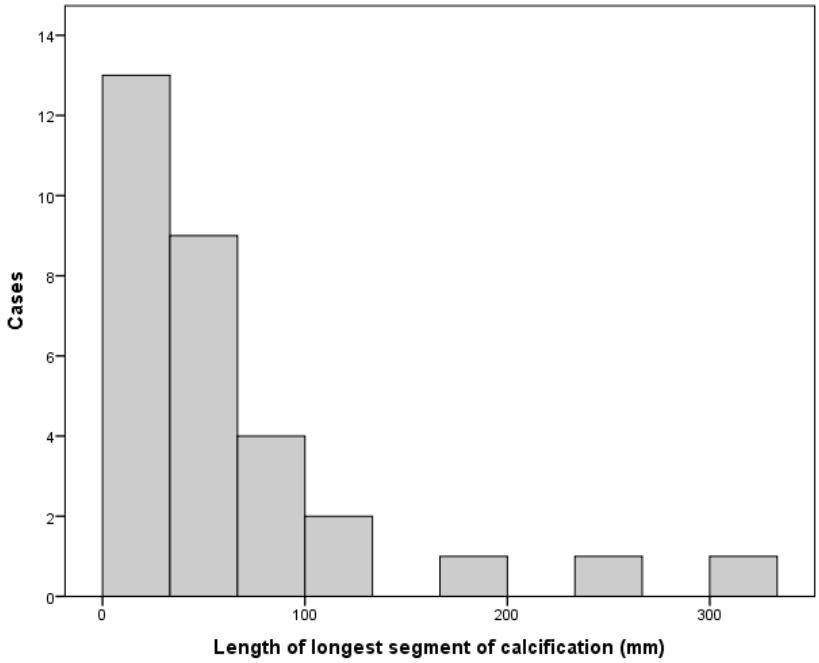

Figure 7.6 Length of longest segment of calcification for each case

The maximum number of quadrants containing calcium in each case was evenly distributed (Figure 7.7), with calcium present in three quadrants or four quadrants in 19 of 38 cases (50.0%). Spotty calcification was seen in 31 of 38 cases (81.6%), with a median of two spotty lesions per case (IQR=4) and a range of 0 to 12 lesions.

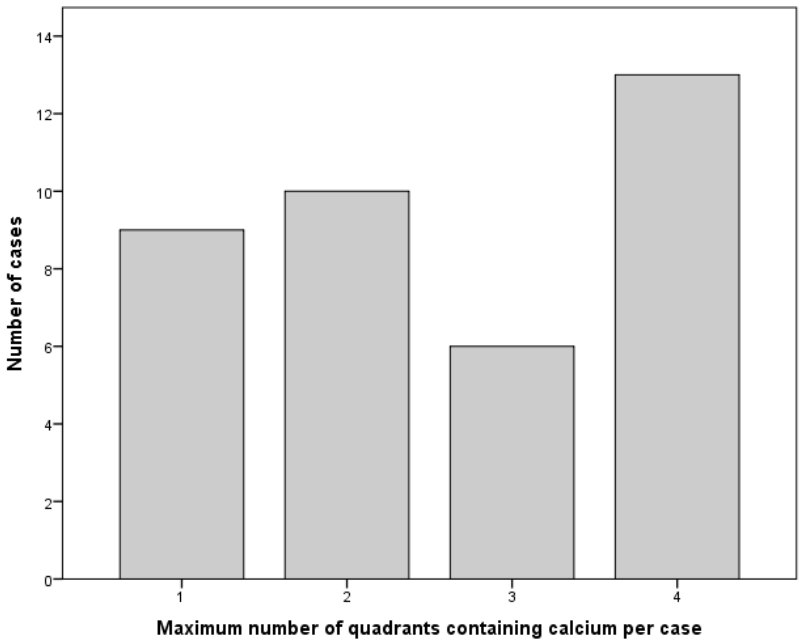

Figure 7.7 Maximum number of quadrants containing calcium for each case

7.4 Discussion

7.4.1 Suitability of peripheral IVUS imaging for core laboratory analysis

This study found that in most cases the IVUS imaging obtained did not meet the study criteria for technical adequacy, with the full set of measurements required for volume analysis available in only 27.5% of sampled frames and a median percentage of fully analysable frames per case of only 24.6%. The low number of frames that were suitable for analysis resulted in only five of 38 of cases (13.2%) fulfilling the criteria for technical adequacy for quantitative analysis.

While there were a number of factors contributing to the high number of frames that could not be analysed, the most important of these was vessel wall calcification, which was present in 56.9% of frames that were excluded for technical reasons. In particular, the ability to accurately measure the EEM was severely limited by the media/adventitia interface being obscured by shadowing artefact caused by heavy calcium. Calcification was present in all cases and extensive, with in 22 of 38 cases having lesions with greater than 50% of the lesion containing calcium. There was also a high prevalence of severe calcification with calcium involving three or four quadrants in 50% of cases. Almost 20% of frames were not able to be analysed due to imaging artefacts and many of these frames also had calcium present. Calcium was likely to be a contributing factor for these artefacts as common IVUS artefacts such as grating lobes are usually more marked when there strongly reflective structures, such as calcium, are present. Cases did not fulfil the criteria for adequacy for analysis due to both an inadequate proportion of analysable frames and also an uneven distribution of analysable frames along the IVUS pullbacks, with many pullbacks having large segments of the lesion with no analysable frames This suggests that IVUS imaging may not be of adequate quality to allow standard IVUS core laboratory methodology to be applied for “whole-of-lesion” volumetric quantification of atheroma burden in patients undergoing endovascular treatment of peripheral arterial disease.

Assessment of post treatment IVUS imaging was performed on the subgroup of cases with technically adequate pre-treatment IVUS imaging and revealed that in all but one case the post-treatment IVUS was inadequate for analysis. The primary factor for the reduction in acceptable frames between the pre-treatment and post-treatment imaging was an increase in the number of frames excluded due to dissection. The results of this study suggest that the technical limitations of IVUS imaging, both before treatment due to calcium and after treatment due to dissection, are such that core laboratory estimation of atheroma volume does not appear to be a practical method for quantifying changes in atheroma volume and therefore may not be useful for studying the effectiveness of atherectomy.

A caveat to this conclusion is that none of the cases that were technically adequate for analysis on pre-treatment IVUS were treated with atherectomy. It is possible that there may have been a

smaller proportion of frames with dissection in cases treated with atherectomy, as this is proposed advantage of the technique; however, post-treatment analyses were not performed in these cases. Even if a reduced amount of dissection had been found after atherectomy in these cases, analysis of changes in atheroma volume would still have been impossible due to the technical inadequacy of the initial pre-treatment IVUS imaging. Atherectomy has been suggested as being of particular benefit with severe calcification(292) and these results suggest that lesions that would most benefit from atherectomy, i.e. those with severe calcification, are also those that are least likely to be analysable using this technique.

None of the previous reports using core laboratory analysis in the peripheral arteries have specifically addressed the issue of whether this type of analysis is technically feasible. None have discussed how IVUS pullbacks should be assessed for technical adequacy for core laboratory analysis. Yin et al.(22), used core laboratory analysis to quantify atheroma volume, arterial remodelling and atheroma eccentricity for entire lesions in the tibial arteries of 42 patients. Atheroma volume was calculated from measurements obtained using standard core laboratory analysis methods but no comment was made on whether there were problems with obtaining measurements for the analysis, despite evidence of extensive calcification, with most cases having calcium involving at least half of the lesion length, calcium arcs greater than 45° present in most cases and a median maximal calcium arc of 285°. Babaev et al.(23), reported atheroma volumes in femoropopliteal arteries of 25 patients using similar methods and again did not comment on whether there were problems with technical adequacy of sampled frames, despite a median maximal arc of calcium of 137° being reported. In the TRUE study, Singh et al.(21), reported using core laboratory analysis methods to investigate atheroma volume before and after rotational atherectomy of predominantly femoropopliteal arteries in 18 patients. These patients represented only half of the potential cases, with the rest excluded from analysis due inability to analyse the IVUS imaging. Unfortunately, no details were provided about the excluded cases, the technical limitations that were encountered in these cases or the criteria for exclusion from analysis. In the cases that were included, analysis was performed on a 20mm segment with minimal calcification (representing one third of the standardised 60mm pullback used in this study), with heavily calcified parts of the lesions that might limit accurate EEM measurements avoided. Although no details were provided regarding how segments were selected for analysis in this study, it is clear that an undefined but substantial proportion of frames in the IVUS pullbacks were compromised by poor image quality. Although not stated specifically by the investigators, a conclusion that can be drawn from the TRUE study is that that whole-of-lesion core laboratory analysis was not possible in most of these patients due to the presence of vessel wall calcium.

The current study found even fewer images to be of acceptable standard than that reported by Meissner at al.(24), who found just under half of the IVUS images to be technically unsuitable. They used a less stringent threshold for rejecting an image for measurement compared to the core

laboratory analysis method used in the current study (calcium involving >90° of the vessel wall vs > 45° of the vessel wall) and when this is taken into account the two results are probably generally comparable. The results of the current study are also broadly in agreement with the inferred results from the TRUE study.

The lack of comment on whether any problems with analysis were encountered due to calcium in the studies of Yin et al.(22), and Babaev et al.(23), is difficult to interpret. It seems unlikely, given the amount of calcium seen with IVUS in these studies, that there were no restrictions in image quality due to wall calcification. The lack of comment suggests that the presence of calcium was not considered a major problem in these studies. It is also possible that the criteria for what constituted an acceptable frame for vessel measurement were different to what is generally applied in core laboratory analysis.

7.4.2 Assessment of technical adequacy of IVUS imaging

The aim of the current study was to assess how many IVUS fames and IVUS pullbacks were technically adequate for atheroma volume estimation. Criteria were required to assess technical adequacy of each frame and each IVUS pullback. Assessment of technical adequacy of each frame was straightforward as the guidelines for IVUS based for coronary atheroma volume analysis are available(231). There is general agreement for this methodology in the coronary arteries. There is no reason to believe that these criteria should not apply to peripheral arteries as the same technical limitations that are present in the coronary arteries, such as calcium obscuring the EEM and other structures such as large branching arteries obscuring or distorting the vessel wall, exist in the peripheral arteries and the differences between IVUS technology used in the coronary and peripheral arteries are minor and would not address these problems. There are no IVUS technologies available that can overcome the problem of calcium in the vessel wall and it is unlikely that there are modifications that can be developed as the total attenuation of the ultrasound beam by calcium is a fundamental limitation of all ultrasound in the diagnostic frequency range.

The most appropriate method for assessing the overall technical adequacy of an IVUS pullback in the peripheral arteries was less clear as there were no criteria currently available for the peripheral arteries. The criteria for inclusion or exclusion of arterial segments in coronary atheroma regression/progression studies are designed for studies that require relatively short segments (between 10 and 30mm) of an artery that are studies over a period of time. These patients typically have mild disease, do not require endovascular treatment and usually have minimal calcification. The proportion of cases that are excluded from this type of analysis is estimated to be about 2% (231). These conditions are unlikely to be the case in the peripheral arteries where more extensive and severe calcification is more common(17).

The goal for IVUS analysis in the current study was volume estimation of the entire lesion, rather than use of a sample segment. This is important if the atheroma burden for an entire artery is required and for assessment of the performance of atherectomy as atheroma removal is unlikely to be uniform throughout a lesion. Excluding calcified segments from atheroma volume estimation might therefore run the risk over-estimating the effectiveness of plaque removal.

The criteria for technically adequacy of an IVUS pullback created for the current study assessed both the overall percentage of frames available and the uniformity of distribution of frames over the lesion length. Uniform distribution was considered particularly important as an IVUS pullback with >50% of frames available may still be unrepresentative of the lesion as a whole if all the technical inadequate frames were grouped together in one segment. Clear differences were seen in the appearances of the cases classified as unsuitable and suitable for analysis as displayed in the line plots in Figures 5.2and 5.3 and this subjective visual analysis suggests that these criteria were effective at identifying cases with higher density and uniform distribution of analysable frames.

This is demonstrated in cases 17 and 23 (Figure 5.3), where case 17 has a higher proportion of frames available for analysis but has less uniformly distribution than in case 23. The gaps between analysable segments are shorter in case 23 than case 17 where there is a gap representing more than a quarter of the lesion with no measurements available. A similar pattern is seen in cases with a high percentage of frames available, e.g. case 12 and 16 (Table 5.3), with case 12 having a lower proportion of frames available for analysis but a more uniform distribution than case 16.

7.4.3 Limitations

The major limitation of this study is the lack of a reference test for atheroma volume to which the IVUS volume estimates could be compared. Such a reference test would have enabled testing of whether the technical adequacy criteria applied in the current study were good predictors of the accuracy of volume estimates. Such a test was not used in the current study and it is uncertain what would constitute an appropriate reference test in this situation.

OCT has higher resolution and superior imaging of calcium compared to IVUS (227, 293) but has a limited depth of view, short pullback length and cannot be used to perform long manual pullback due to need to clear blood from the lumen. These limitations make it impractical as a reference method for the arteries and lesions examined in the current study. MRI has been used to study vessel area(24), atheroma composition and eccentricity (294, 295) and reproducibility and reliability(24, 296). Comparison of MRI and IVUS measurements of vessel area in the SFA is limited by the problems of IVUS measurements when calcium is present that have already been discussed(24). Although most studies have examined short lengths, it has been used in lesions greater then 20cm long (296) and so has the potential to image the extensive type of lesions included in the current study. CTA has also been used to study atheroma composition and could

potentially be used to estimate atheroma volume(297). The use of these modalities for atheroma volume estimation in the peripheral arteries is still experimental and there is no consensus on whether any can be considered as reference tests.

In the absence of a reference test, some inferences can be made regarding the appropriateness of the technical criteria used to assessment the IVUS imaging for each case by comparing the results for cases assessed as adequate and inadequate in the current study. Cases that were inadequate for analysis had significantly more calcium than the cases that were adequate. As there is a clear association between calcification and severe disease (17), it would be expected that parameters associated with severe disease, such as negative remodelling(83) and eccentricity(80), would be at least as severe in this group as in the group that was adequate for analysis. In fact, the comparison between the two groups in Table 5.4 found that cases that were inadequate for analysis had a trend toward less negative remodelling and lower atheroma. If these results were representative of the entire lesions in this group it would suggest that the technically inadequate cases had less severe disease than the technically adequate cases, despite having more severe calcification. Whilst this is possible, it seems more likely that disease severity was underestimated in the technically inadequate group and that the analysis from the available IVUS imaging was not representative of the lesions as a whole.

It is possible that the thresholds applied might be either too high and or too low. Reducing either threshold by itself would have had little effect on the number of cases assessed as adequate for analysis as no extra cases would have been included if the threshold was set at ≥25% of total frames or if the distribution criteria was set to allow cases with only half of the eight segments to be analysed frames. If both criteria were lowered to these thresholds then an extra seven cases would have been assessed as technically adequate for volume estimation (cases 10, 18, 19, 20, 30, 33 and 34 in Figure 7.2). However, when these cases are reviewed visually it is difficult to be convinced that these represent sufficient samples for adequate analysis. If the threshold was increased to ≥75% of total frames the number of acceptable cases would drop to three and would further strengthen the conclusion that IVUS is not a viable analysis method for volume estimation.

The use of manual pullbacks rather than mechanical pullback with a motorised sled is also a potential limitation of the current study. Mechanical pullback was used in previous studies of volumetric analysis of peripheral arterial IVUS(21-23) but these studies were restricted to short lesions. As discussed in Chapter Two and Three of this thesis, manual pullback was necessary due to the length of the lesions being treated. The lengths of pullbacks were able to be accurately delineated on IVUS by the use of the radio-opaque ruler and identification of fiduciary branches. The unknown variability is the pullback rate and therefore the interval between sample frames. This variation may affect the regularity of the distance between sampled frames and is more likely to be significant in shorter lesions. This is likely to have less effect in long lesions due to averaging

out of any errors. The overall effect of this variability on volume estimates is unknown.

7.5 Summary

The high proportion of IVUS frames in which full analysis could not be performed resulted in most IVUS pullbacks being unsuitable for analysis. This suggests that there are significant limitations to performing quantitative core laboratory analysis of entire lesions in the femoropopliteal arteries. This type of analysis is therefore unlikely to be suitable for atheroma volume estimation and is therefore unlikely to be suitable for applications such the assessment the performance of endovascular treatments such as atherectomy.

8 CONCLUSIONS

IVUS is a mature technology that can accurately and reliably characterise arterial anatomy and pathology. Although there is some data suggesting the use of IVUS may result in an improvement in outcomes, it's role in peripheral endovascular interventions is currently unclear(16) and this is reflected in the low levels of IVUS usage that have been reported in lower limb arterial interventions(15).

The research presented in this thesis investigated various aspects of using IVUS in endovascular interventions on the femoropopliteal artery. The primary study of this thesis was performed to investigate whether the use of both IVUS and angiography to guide endovascular intervention would result in a lower rate of binary restenosis at one year compared to using only angiography. This study also provided an opportunity to use IVUS to investigate other aspect of interest in endovascular treatment including the grading of vascular calcification, the classification of post-treatment dissection and the potential for using IVUS to estimate atheroma volume.

In the primary study reported in Chapters 3 and 4, a RCT was undertaken to test whether participants who had treatment guided by IVUS in addition to angiography (the treatment group) would have a lower rate of restenosis compared to those with treatment guided by angiography alone (the control group). Interim findings of one-year follow-up on 70% of the target sample found a significant reduction in binary restenosis in the treatment group compared to the control group (freedom from binary restenosis of 77.8% in the treatment group and 56.6% in the control group, p=0.007). These are findings are interim in nature and more final conclusions must wait for results of the complete sample, but they are certainly suggestive that having IVUS available during endovascular interventions confers a benefit in relation to restenosis. IVUS imaging resulted in changes in treatment in almost 80% of cases in the treatment group, with an increase in treatment length or device size making up over 80% of these cases. Randomisation to the treatment group (those who had guidance of the intervention with both IVUS and angiography) and use of DCB were both predictors of reduced rate of restenosis. Subgroup analysis of participants treated by DCB showed a significantly lower rate of restenosis in the treatment group, suggesting that the use of IVUS may assist in optimising the use of DCBs with resulting lower restenosis rates. This conclusion is speculative as it is based on observations from sub-group analysis and cannot be proven from the data available. These findings, however, are hypothesis generating and suggest that a larger trial designed to test the use of IVUS in patients being treated with DCB would be warranted.

In relation to the second research question this thesis, the results of the study described in Chapter 5 found that while there was a trend for length and arc of calcium to increase with the grade of severity in all the scoring systems, the only significant difference in an IVUS parameter between

mild and severe grades of calcium was in arc of calcium for the Fanelli system(184). No difference was found for any of the angiography-based calcium scoring systems. The angiography-based scoring systems agreed completely at allocating cases to mild and severe grades and there was good agreement between these systems and the Fanelli system. These results suggest that none of the angiographic-based systems were good at differentiating between more and less severe calcium. This may relate to the poor sensitivity of angiography for detection of calcium found in the current study, which was in agreement with previous studies(9, 10, 78). The superior performance of the Fanelli scoring system, which utilises CTA and angiography, probably reflects the superior sensitivity of CTA for calcium detection compared to angiography. Currently available studies validating calcium scoring systems have been restricted to angiographic systems(182, 209) and consideration should be given to including CTA and IVUS in future calcium validation studies. The relatively low agreement and reliability found between raters for all of the scoring systems raised concerns regarding the use of any of these systems in clinical practice. The relatively small sample size of this study is a limitation and repeating inter-rater reliability testing in a larger sample is required to confirm these findings.

The results of the study described in Chapter 6 relate to the third research question of this thesis: are there significant differences in IVUS anatomical parameters for severe dissection between the NHLBI and Kobayashi systems and what is the agreement and reliability for allocating cases between raters? There were no differences in IVUS dissection parameters for severe dissections between the Kobayashi and NHLBI classification systems and good agreement and reliability was found between the systems, indicating that they perform in very similar ways. This suggests that results from the two systems are likely to be comparable. It was hypothesised that the Kobayashi system would have superior inter-rater reliability due to its simpler design and while this was the case, the difference was small and the agreement and reliability of both systems was only fair to moderate. This raises concerns about whether either system has sufficient reliability for clinical use. No difference was found for IVUS measurements between mild and severe dissection within each system. A contributing factor for this result may be the limitations of angiography for characterising dissection(8) and the use of IVUS in future studies validating these classification systems should be considered. A limitation of the current study was the small sample sizes for some dissection grades and a larger study would be useful to confirm these findings.

The results of the study described in Chapter 7 relate to the fourth research question of this thesis: how many cases undergoing IVUS during peripheral endovascular intervention have an adequate proportion of suitable images for performing atheroma volume analysis? In this study, only 27.5% of frames sampled were technically adequate for measurement and as a result only 13.2% of cases had enough cases to allow analysis. Calcification was the most common cause of images being unsuitable for measurement. This suggests that IVUS imaging is not suitable for volume estimation in the peripheral arteries, a finding that agrees with the conclusions of the study

comparing MRI and IVUS imaging of the SFA by Meissner et al.(24). Further investigations of alternative methods such as MRI should be undertaken as these may be more suitable for obtaining volume estimates in the peripheral arteries.

In conclusion, the interim results of the RCT undertaken as part of this thesis suggest that the use of IVUS may reduce restenosis rates in femoropopliteal endovascular interventions. The optimisation of DCB therapy by IVUS may be a possible mechanism for this improvement. However a specific study or a mediator analysis is required to confirm this. The use of IVUS also enabled the acquisition of quantitative data that allowed the performance of calcium and dissection classification systems to be investigated. This information suggests that current angiography-based systems may not be good at categorising severity of both calcification and dissection. The degree of inter-rater reliability and agreement was also disappointingly low in the current studies. These results suggest that the conclusions of previous studies that have examined the clinical impact of calcium and dissection may be less reliable than expected. Confirmation of this finding by studies with larger sample sizes is required. The results of the current studies suggest that the inclusion of IVUS imaging into future studies is required to ensure that calcium and dissection severity are adequately characterised. And finally, IVUS imaging was not technically adequate for the performance of volume analysis in most cases and the estimation of atheroma volume using IVUS does not appear to be feasible in femoropopliteal arteries.

Overall, the results presented in this thesis suggest that IVUS can assist with increasing our understanding of peripheral arterial endovascular interventions. There are likely to be important benefits for research studies from the use of IVUS to acquire quantitative data and the inclusion of IVUS in future peripheral endovascular research is strongly encouraged. The interim results provided by the RCT reported in this thesis are very encouraging. The time may have arrived for IVUS to become part of standard peripheral arterial endovascular practice rather than being solely a research technique.

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APPENDIX 1 PERIPHERAL ARTERIAL DISEASE AND ENDOVASCULAR TREATMENT TECHNIQUES

A1.1 Lower limb peripheral arterial disease

PAD is the accepted terminology for the disease processes that cause stenosis or occlusion in the peripheral arteries(298). It is most commonly applied to atherosclerotic disease affecting the lower limbs and this is the meaning that will be applied in this review. Lower limb PAD is a major and growing problem and is the third leading cause of morbidity from atherosclerotic disease(299). The global prevalence of PAD was estimated at over 200 million in 2010 and was estimated to have increased by 23.5% in a decade since 2000(299). For two million of these people this will result in will a major limb amputation and 45 million will die from coronary heart disease or cerebrovascular disease. PAD is primarily a disease of old age with prevalence rates from one study finding a prevalence of 2.5% in subjects aged 50-59 years, rising to 14.5% for those over 70 years(300). PAD is an under-diagnosed disease with between 10% and 50% of patients identified with intermittent claudication in epidemiological surveys having never seen a doctor in regard to their symptoms(222).

The clinical consequences at PAD vary greatly depending on presentation. Chronic PAD presents as either intermittent claudication, defined as muscle discomfort due to exertion and relieved by resting within 10 minutes(222), or as CLI, defined as ischemic rest pain and/or ulcers attributable to arterial disease(222). The prevalence and consequences of these conditions vary greatly. Only about 1-3% of patients with chronic PAD present with CLI, with the rest presenting with intermittent claudication (301). About 20-50% of patients will have asymptomatic intermittent claudication, 30-40% will have atypical leg pain and 10-35% will have typical claudication symptoms(301). Even though intermittent claudication is the milder form of PAD patients do not necessarily follow a path of initial presentation with claudication followed by development of CLI. In fact, in about x% of case presenting with CLI have not been previously diagnosed with PAD.

The Rutherford and Fontaine systems have been developed to categorise PAD(222, 302). These are both based on severity of clinical symptoms. The Rutherford system is more widely used in Australia and is the classification used in the candidate's host institution and will be used in the research presented in this thesis. Claudication severity is graded by decreasing walking distance and a reduction in post exercise ankle pressures (303). Severe intermittent claudication can be considered as representing a walking restriction that is markedly life style limiting and is usually considered to be

represented by a pain free walking distance of <100-200m. Most patients diagnosed with intermittent claudication will remain stable without significant clinical deterioration but a quarter will develop worsening symptoms(222). Amputation in patients with intermittent claudication is uncommon, occurring in 1% to 3.3% in the five years after diagnosis(222). The recommended treatment for patients with mild and moderate severity intermittent claudication is exercise (ideally in a supervised exercise program)(304, 305) and revascularisation is generally not recommended, unless exercise and risk factor modification are unsuccessful, due to the risks of intervention and the low risk of significant clinical deterioration(304). Patients with severe intermittent claudication are much more likely to undergo revascularisation due to the more severe life-style limitation implied by the shorter pain-free walking distance and the inability to undertake significant exercise. Even though the limb-related clinical prognosis for the majority of patients with claudication is relatively benign there is a significant risk of associated cardiovascular morbidity and mortality. There is a 20% five-year risk of non-fatal myocardial infarction or stroke and a 10-15% five-year all-cause risk of death, with 75% of this due to cardiovascular causes(301). There is no consensus on the threshold for when to offer revascularisation in claudication or on the best mode of treatment

CLI has very different consequences to claudication. One year mortality and morbidity is high with 30% of patients receiving an amputation and a death rate of up to 25% (301). For these reasons revascularisation is generally offered to patients who are medically fit for the procedure although there is also no consensus on the best mode of treatment.

A1.2 Current methods of endovascular treatment in PAD

A1.2.1 Development of catheterisation and endovascular interventional techniques

Endovascular arterial interventions are a product of the phenomenal expansion in technological capability that has occurred since the middle of the twentieth century. Its basis is the concept of safe access to, and catheterisation, of the arterial component of the circulation.

The concept of catheterisation of internal body spaces is very old, with bladder catheterisation being first recorded in Egypt in approximately 3000BC(306). Harvey catheterised a cadaveric IVC in 1651 and the Hales performed the first cardiac catheterisation in 1711, on a horse (306). Bernard is credited with first use of the term “catheterisation” in 1844 when reporting temperature measurements within a horse’s heart using a glass thermometer (307). Chauveau and Marey introduced the use of

rubber catheters for accessing the veins, arteries and heart in 1861 (307).

The ability to image the blood vessels is central to the development of endovascular interventions and the key advances for this were Roentgen's discovery of X-rays in 1895 (308, 309), the first arteriogram produced on a cadaver using chalk injected into an artery in 1896(306) and the development of less toxic organified iodine contrast media in 1929 (310). Access to the vasculature up to this time had been by direct puncture, however Seldinger's development of an easy and safe method of intra-arterial access in 1953(311) enabled the beginnings of endovascular diagnosis and treatment as we know it today. The endovascular treatment era can be dated to the publication of Dotter and Judkins' 1964 landmark paper(312) describing catheter based transluminal dilation of arterial occlusive disease. It took some time for endovascular treatment to become an accepted therapy and it was not until the development of balloon angioplasty by Gruentzig in the late 1970s(223, 313) that a clinically viable therapy became available. The development of over-the-wire technology(314) and exchangeable systems(315) further refined angioplasty technique and in the 15 years after Greuntzig's first angioplasty there was a rapid expansion in the use endovascular treatment with the widespread adoption of PCI as the primary treatment for CAD, and the development of a wide range of treatment technologies into coronary endovascular practice(228). Further advances were achieved with the introduction of drug eluding technology in the early 2000s(316).

Even though the first endovascular treatments by Dotter were performed on patients with peripheral arterial disease, the adoption of endovascular treatment in peripheral arteries was much slower than in cardiology. The introduction of new treatment technologies to peripheral endovascular therapy has usually been 5-10 years after introduction to coronary practice. For example the first RCT confirming the superiority of BMS over plain balloon angioplasty in the coronary arteries were published in 1994(317, 318) while the equivalent trial in the femoral arteries was not published until 2006(203).

While the proportion of patients treated with PCI compared to bypass surgery for CAD has been much greater for some years(319), this trend was delayed in PAD and only recently has endovascular treatment become the first choice in the majority of procedures to treat PAD(1). The increased use of endovascular procedures has resulted in an increase in the total number of procedures for treating PAD, with total cases doubling in the 20 years between 1990 and 2010(1, 320) while the number of endovascular procedures has increased threefold and the number of open bypass procedures decreasing by almost half(1). This trend has not been restricted to the USA with recent data from Korea showing the number of endovascular procedures more than doubling

between 2004 and 2013 and the number of bypass procedures decreasing by 39%(321).

Revascularisation may be by performing bypass surgery or endovascular intervention, however there is no consensus on the best method of treatment(213). The only large RCT that has compared surgical and endovascular revascularisation in femoropopliteal disease is the BASIL study, which compared both methods in CLI patients (322). This study found that amputation survival at six months was equivalent for both methods and that endovascular revascularisation was cheaper, had lower procedural morbidity. There was a trend to better long term survival and freedom from amputation (3-5 years) in the surgical group (322) and a seven-month increase in survival for patients who lived for more than two years after surgical revascularisation (323). The BASIL data is now quite old (recruitment concluded in 2004) and the only endovascular treatment used was PTA with a plain balloon (plain angioplasty). Since this time a wide range of endovascular therapies have become available for use in the peripheral arteries, most of which have demonstrated superior performance to plain angioplasty. It is unclear how surgical bypass and current endovascular treatments compare due to the lack of comparative data. The evidence base for clinical decision-making is further clouded by the lack of RCTs comparing surgical and endovascular revascularisation in patients with claudication.

There continues to be a paucity of data. A meta-analysis from 2013 of studies comparing surgical and endovascular revascularisation found insufficient evidence to recommend one method over the other (324). This meta-analysis identified four RCTs (the BASIL trial, which numerically dominated the analysis, and three much smaller trials (325-327)) and six non-randomised observational studies (328-333). It found that endovascular treatment resulted in lower procedural morbidity while surgical treatment had better long-term durability. For these reasons, the authors suggested that endovascular treatment may be a better option for patients with significant co-morbidities whilst surgical bypass may be preferred for fitter patients. In 2015 an update was published from the TASC Steering committee acknowledged the low level of evidence available but conditionally recommended an endovascular first approach in less fit patients, dependent on a range of factors including lesion complexity, patient condition, availability of a vein conduit and local expertise(334).

A1.2.2 Current status of peripheral endovascular interventions

Currently available endovascular treatments include plain angioplasty, drug-coated balloon (DCB) angioplasty, BMS, drug-eluding stents (DES), covered stents (also termed

stent grafts) and atherectomy (using a variety of different technologies). There is wide variation in availability of technologies within and between countries. All of these technologies are available in Australia however the range of options within these broad technology classes may be more limited (such as atherectomy) than in some other jurisdictions. The quality and quantity of evidence supporting the use of these technologies is highly variable as will be discussed below.

A1.2.3 Plain angioplasty

Greuntzig's invention of the double lumen balloon in 1975(313) allowed the development of plain balloon angioplasty as a practical therapy and this became the basis of endovascular treatment. Angioplasty works by increasing the lumen area in a segment of stenosed artery by stretching the vessel wall and by cracking and compressing the stenotic plaque(27, 109-111, 335, 336). Until recently plain balloon angioplasty has been the primary peripheral endovascular treatment modality. It is however associated with high rates of treatment failure with restenosis rates of 40-43% and target lesion revascularisation (TLR) of 27% reported (337, 338). The high rate of treatment failure after plain balloon angioplasty is due to residual stenosis and late restenosis. Residual stenosis is due to a large dissection of plaque limiting the lumen area or when there is elastic recoil (the reversion of the vessel to its original dimensions after dilatation)(339). Late restenosis is due to lumen reduction caused by neointimal hyperplasia (NIH) (340)and negative remodelling(83, 101). The underlying cause of NIH is an inflammatory response induced by the barotrauma associated with dilatation(341),resulting in a phenotypic change in the vascular smooth muscle cells, which proliferate and migrate into the intima driving the development of NIH (340-342). Negative remodelling is poorly understood but thought to be due to constrictive collagen bands that form as part of a modification process in the adventitial extracellular matrix driven by adventitial myofibroblasts activated by the trauma of angioplasty(99).

The limitations of plain balloon angioplasty have led to a proliferation of peripheral endovascular therapies aimed at improving treatment success rates. These therapies have aimed to address the problems of residual stenosis and late restenosis by moulding the lumen open (in the case of stents), reducing the inflammatory response (anti-proliferative drug technologies), isolating the vessel wall from the lumen (covered stents), or reducing the plaque volume and modifying plaque composition to minimise dilatation related trauma (atherectomy).

In the last ten years these alternative treatment methods have become more widely used as more evidence of improved clinical performance become available. Although there are

no reliable Australian data regarding the proportion of treatment types, it is likely that in the majority of femoropopliteal procedures the definitive treatment is no longer plain angioplasty. Dilatation with a plain balloon is still a fundamental component of most endovascular procedures as an adjunct to other technologies, e.g. pre-dilatation by plain balloon prior to use of DCB is recommended by manufacturers(245) and is usually performed due the desire for adequate vessel preparation before drug delivery(263, 343).

A1.2.4 Bare metal stenting

Stents were developed to address the problem of residual stenosis by providing a scaffold to maintain an adequate lumen if post-angioplasty dissection or elastic recoil occurred. The first intra-luminal placement of a stent occurred in 1986 in the coronary artery using a self-expanding stent(344) and in 1987 Palmaz implanted the first balloon-expandable stent in a peripheral artery(345). RCTs in the early 1990s demonstrated the superiority of the Palmaz-Schatz stent over plain angioplasty in the coronary arteries (317, 318) with FDA approval being gained in 1994. Within four years >80% of PCI were performed using balloon-expandable stents (346). This rapid adoption of endovascular stenting was not repeated in the peripheral arteries. The use of balloon-expandable BMS in peripheral interventions has primarily been in the iliac arteries as problems with external compression, deformation and fracture in the femoropopliteal arteries (40, 347) resulted in no improvement in outcomes over plain angioplasty (348). Stenting in the femoropopliteal arteries only became an accepted therapy with the development of nitinol (a nickel-titanium alloy which has thermal memory characteristics and is more flexible) self-expanding stents and the completion of randomised trials that demonstrated clear evidence of improved outcomes compared to plain angioplasty (203, 204).

Although stents can successfully provide a scaffold for lesions that have been resistant to angioplasty they are vulnerable to restenosis due to NIH. This is due to multiple factors including acute trauma during stent expansion, de-endothelisation and chronic inflammatory response(340, 349). The presence of the stent disrupts laminar flow which also contributes to the development of NIH (350). Restenosis with BMS remains an issue (12-month restenosis rate as high as 32 to 37%(203, 215)) and there is no consensus on how nitinol BMS fit into treatment algorithms in the femoropopliteal arteries. The peak probability of ISR is at one year, after which the risk of ISR gradually declines (351). The type of lesion being treated appears to have an effect on outcomes of stenting with chronic total occlusion (CTO) having higher rates of ISR and occlusion than stenotic lesions (352). Although nitinol stents are more flexible than balloon-expandable stents they still are at risk of kinking and fracture(353, 354).

Stenting can used as a primary treatment, i.e. where a stent is intended to be used from the onset of the procedure, or as a secondary, adjunctive treatment (so-called “bail-out” or “spot” stenting) when there is a technical problem with angioplasty such as flow-limiting dissection or residual stenosis due to recoil (40). Even with self-expanding stents adequate pre-dilation by plain balloon angioplasty is recommend and post-dilation may also be required for dilation-resistant lesions(40).

A recent meta-analysis has confirmed the superiority of BMS over plain angioplasty (primary patency OR 2.83, 95% CI=1.04-7.69, p<0.01) (348) although this superiority appears to be lost after two years(355). It is unclear how BMS treatment compares to other treatment technologies due to the lack of comparative studies and analysis using network meta-analysis techniques is mixed with one analysis finding insufficient data to assess the performance of BMS in relation to newer technologies such as DCB and DES (348), another found BMS to have significantly higher LTR rates than DCB or DES (356) and another concluding that BMS had higher TLR rates than DCB but insufficient data in relation to DES and covered stents(357).

A1.2.5 Drug-coated balloon angioplasty

Drug-coated balloons (DCB) are angioplasty balloons that are coated with an anti-proliferative drug intended to disrupt the development NIH and so reduce the rate of restenosis(358). All DCBs used in the peripheral arteries utilise paclitaxel as the active pharmaceutical. Paclitaxel is a tubulin-targeting, cytotoxic drug that binds to the cell microtubules and blocks the progression of mitosis, leading to apoptosis without cell division(359). In peripheral angioplasty, the target cells of paclitaxel are the vascular smooth muscle cells. The phenotypic change in the vascular smooth muscle cells is suppressed by disrupting mitosis and so reduces the speed and severity of NIH (358, 360).

The first peripheral trials of paclitaxel DCB angioplasty were performed using the Paccocath balloon in 2004-2006(201, 361) and DCBs have now become widely available throughout the world. Multiple systematic reviews and meta-analyses have been published in the last few years assessing the performance of DCBs and have concluded that outcomes (including LLS, binary restenosis and TLR) are improved with DCBs when compared to treatment with plain angioplasty (337, 338, 348, 356, 362-364).

An important finding from these reviews was the lack of a class effect for paclitaxel

DCB(338). There are a number of characteristics that may vary between different DCBs that can affect the efficacy of the treatment. These include the form of paclitaxel used (crystalline vs. non-crystalline), the dose of paclitaxel (higher rates of binary restenosis and TLR were found with balloons using a lower dose of paclitaxel(338)), and the excipient carrier used to assist transfer of the drug from the balloon to the vessel wall. Application of the DCB is also critical with manufacturers and expert advice stressing the need for correct sizing and careful technique to ensure good balloon to wall apposition and adequate drug delivery(245, 343).

There is a lack of comparative data for outcomes for DCB in relation to BMS, covered stents and DES. Network meta-analysis suggests that DCB has lower TLR rates than BMS(356, 357) but insufficient data to asses effectiveness compared to covered stents and DES(357).

A1.2.6 Covered stents

A covered stent (also called a stent graft or an endoprosthesis) is a stent covered in a synthetic material that separates the intima from the lumen. These stents were developed as a means of reducing ISR by isolating the endothelial cells from the circulating blood and interrupting the cascade of events precipitated by platelet activation. Results for the initial version of the Viabahn covered stent, incorporating expanded polytetrafluoroethylene (ePTFE) material covering with a flexible ring stent design, were disappointing with TLR or primary patency rates that were not significantly different to those achieved with BMS (365). Heparin bonding has been shown to reduce thrombosis rates in ePTFE bypass grafts (366) and the addition of heparin bonding to the interior of the Viabahn stent (43, 367) reduced the risk of thrombosis, resulting in significantly improved primary patency rates of up to 88% at one year (43). RCT data confirmed that primary patency rates were significantly higher for heparin bonded covered stents in comparison with BMS at one year (70.9% vs 55.1%(368)) and two years (63.1% vs 41.2%(369)). A particular feature of heparin bonded covered stents is that the patency rate does not alter as much with increasing stent length as is found with BMS(369, 370). This is in contrast to BMS where the patency rate decreases as the stented length increases (370, 371). This difference in performance is most marked when a subgroup of long lesions (>20cm) was analysed finding the covered stent patency at two years to be 65.2% compared to BMS primary patency of 26.7%. There is no comparative data for the performance of covered stents in compared to DCB or DES.

A1.2.7 Atherectomy

Atherectomy refers to the removal of plaque from an occlusive lesion by an endovascular device. All atherectomy devices are passed along an artery and remove plaque as they traverse the lesion. They are a heterogeneous group of devices usually categorised by the mechanism of action an include: directional devices, which use a cutting device to excise an arc of plaque with each pass, ablative devices that use laser light to remove a circumferential area of plaque, rotational devices that remove a circumferential area by spinning cutting blades, an abrasive burr or screw-like mechanism at high speed, and orbital devices that use an abrasive head that spins at variable speed in an orbital fashion(228, 372, 373). Each category of device provides a unique mix of attributes but generally share some important characteristics with other categories. The directional and orbital devices both have the ability to remove an area of plaque larger than the device itself whereas the lumen created by the ablative and rotational devices is limited to the size of the device. The directional devices are the only ones that can selectively remove plaque from areas of a vessel circumference(372, 373).

The theoretical basis for treatment with atherectomy is 1) the reduction in plaque burden, allowing lumen increase either without balloon angioplasty or with less traumatic balloon angioplasty, and 2) plaque modification, primarily by removal of hard plaques and calcium to improve wall compliance, to allow less traumatic dilatation, avoid severe dissection, reduce the risk of over-stretching and facilitate drug diffusion when using DCBs (373-377).

The main safety concerns with these devices are the potential for distal embolization and for damage to the vessel wall (including dissection and perforation)(169, 171, 272, 374). Distal embolization is mitigated by removal of plaque, in the case of cutting technologies such as directional and rotational blade devices, or reduction of the plaque to particles small enough to pass through the capillaries, in the case of ablative devices such as those using an abrasive burr or laser. The risk of distal embolization is greatest with the cutting devices but the use of distal embolic protective filters is advised even for ablative devices(373, 374). Adventitial injury has been recognised as an important contributor to restenosis and fibrotic scarring of the vessel wall (99, 378). Samples from the coronary artery treated with directional atherectomy suggest that the media and adventitia is damaged in about 30% of cases(271). Specimens from femoropopliteal lesions treated with directional atherectomy found adventitial tissue was present in 52% of 116 samples and that this resulted in a significantly higher rate of restenosis compared to cases without adventitial injury (171).

Proponents suggest that vessel preparation with atherectomy, paired with plain angioplasty or DCB angioplasty, will significantly reduce restenosis and lower the rate of re-intervention(377, 379) , however the evidence that atherectomy improves outcomes compared with other treatments in both the coronary(380-382) and peripheral circulations(373, 383, 384) is scant.

A Cochrane review from 2014(384) found only four RCTs investigating atherectomy of the peripheral arteries (three studies of directional atherectomy(385-387) and one of orbital atherectomy(292)). All were classified as of poor quality with significant methodological flaws and none showed a significant improvement in patency rates for atherectomy treatment compared to balloon angioplasty. It should be noted that in three of these studies the comparison was between atherectomy alone and balloon angioplasty(385-387). In only one study was balloon angioplasty compared with combined atherectomy and angioplasty(292), this was predominately of the infra-popliteal arteries (>90%) with no significant difference in TLR rate between the groups. A systematic review and meta-analysis, also from 2014, also concluded that technical success was similar between atherectomy and plain angioplasty, that the bail-out stent rate was similar, and there was no clinical outcome benefit from debulking with atherectomy(383). A more recent review from 2017 also agreed that there was no evidence of superiority of atherectomy compared to plain angioplasty or stenting.

In a study published since this review (388), three treatment arms (directional atherectomy vs DCB+BMS vs. plain angioplasty+BMS) were compared with DCB+BMS superior to the other two treatments. A small study of laser atherectomy+DCB vs DCB showed higher 1 year patency for DCB alone(389). A larger, multi-centre study compared clinical outcomes for directional atherectomy combined with DCB vs DCB alone and found improved technical success compared to DCB alone but no significant difference in clinical outcomes (268).

Despite the attractive conceptual models for the benefits of atherectomy, it is still an unproven technology. To date the level of evidence has been poor(373, 383, 384) and large, high quality trials comparing atherectomy combined with current treatment technologies such as DCB are required.

A1.2.8 Drug-eluting stents

Drug-eluting stents (DES) have been devised to address the substantial restenosis rate that occurs after treatment with BMS. The concept of a DES is simple: an anti-proliferative agent is coated onto the stent struts and is slowly released into the arterial

wall to impede the vascular smooth muscle proliferation induced by stent related inflammation and thereby retard the development of NIH(340, 390, 391). By this means the primary role of the stent as a scaffold to maintain patency is achieved with reduced risk of developing later restenosis.

Sirolimus, an inhibitor of mammalian target of rapamycin (mTOR), is used in coronary DES and has been highly successful at minimizing restenosis, becoming the dominant PCI therapy(316, 319, 341). Trials of sirolimus or analog-based DES in the peripheral arteries were disappointing with results that were no better than BMS (392-394). These results were thought to be due to the short time period that the active agents were resident in the arterial wall(395). Paclitaxel remains in the vessel wall tissue for more prolonged periods and both currently available peripheral DES utilise paclitaxel as the active agent(250, 396). The Zilver PTX stent has demonstrated superior results at 5 years in comparison with plain angioplasty (397) and a comparison of the Zilver PTX and Eluvia stent confirmed non-inferiority of the two devices(398) have had more success. In a complicated study design the Zilver PTX RCT tested provisional stenting (stenting after unsuccessful plain angioplasty) by randomising treatment between DES and BMS and found superior primary patency for DES provisional stenting. Unfortunately, there is no data comparing DES and BMS for primary stenting.

There is a lack of comparative data for outcomes for DES in relation to BMS, DCB and covered stents and the results of network meta-analysis showed no significant advantage for DES over DCB, however there has been no direct comparison of DCB and DES and the paucity of data limits the confidence of this conclusion (356).

APPENDIX 2 DEVELOPMENT AND FEATURES OF IVUS TECHNOLOGY

A2.1 History of development of IVUS

Technological advances in electronics and sonar during World War 2 provided the opportunity for medical researchers and engineers to develop viable ultrasound based diagnostic equipment and techniques. By 1952 Wild and Reid had developed a handheld scanner capable of producing anatomic imaging(399) and by 1955 they had created a rotating device capable of use in a luminal space, specifically the rectum(400). In 1956 Czieszynski developed an ultrasound catheter capable of imaging within the heart in animals(401) and gradual development was seen through the 1960's. This culminated with the development of the first fully cross-sectional intraluminal catheter by Bom et al., in 1972(402). This device produced a 360° axial image within vessels using a multi-element phased array and was the first IVUS device recognisably similar to the equipment used today. Due to its large size, low frequency transducer (5.5MHz) and lack of flexibility its use was limited to investigating intra-cardiac anatomy.

It would be another 15 years before smaller and more flexible catheters were developed capable of being used in routine clinical settings. These devices utilised either a rotating transducer or a phased array configuration with sufficiently high transmission frequencies (20-45MHz) to produce high resolution, 360° axial images(48, 403, 404). These devices were able to be delivered via 5 or 6Fr access sheaths and to be guided using standard 0.014" or 0.018" guide wire systems and were therefore suitable for clinical use in the aorta, coronary and peripheral arteries. IVUS catheters using a frequency of 20-45 MHz produce an image with an axial resolution of approximately 150μm(405). Lateral resolution varies with the depth of imaging but is approximately 250μm in coronary arteries(405).

A2.2 Operation and features of IVUS equipment

Rotational IVUS devices achieve a 360° field of view by rotating a single transducer within the catheter or by using a fixed transducer and rotating an acoustic mirror set at 45° to propagate the ultrasound beam perpendicular to the catheter(400, 405-408). The rotating parts are enclosed within the catheter by a thin membrane designed to allow good transmission of sound whilst protecting the catheter and the vessel from potential damage due to high rotational velocities. Typically, rotational IVUS transducers are available in the 30 to 45 MHz frequency range and rotate at 1800 RPM producing a frame rate of 30

frames a second. Rotating IVUS catheters use short guidewire monorail configurations of less than 2cm with the transducer placed behind this, as there is insufficient room to house the transducer shaft and a lumen for the guidewire within the IVUS catheter.

Phased array transducers use an array of 32 or 64 perpendicularly directed elements arranged in a band around the circumference of the catheter(48, 400, 404, 405). Control circuitry within the catheter dynamically controls the transducer array. This allows the use of a “synthetic aperture array” function, in which the number of elements receiving reflected signals can be selectively increased or decreased(335). This allows a degree of beam focussing to be created, narrowing the effective beam during signal reception and resulting in improved lateral resolution of structures further away from catheter(192). These transducers produce an image by activating groups of elements in sequence around the catheter at a frame rate of up to 30 frames per second. Phased array IVUS catheters either use a long monorail (e.g. 20 cm) or a full length over-the-wire configuration with the transducer positioned within 5mm of the catheter tip.

Phased arrays are more robust than the rotating types due to the lack of moving parts(409). The location of the transducer close to the tip allows imaging closer to an occlusion or a very narrow stenosis. The long monorail and over-the-wire configurations also allow greater support compared with the rotational configuration, adding to the robustness of the design. Phased array catheters have lower frequencies (10-20 MHz) than the rotating types and so produce images with lower resolution. In addition the phased array design results in a ring-down artefact (due to vibration of the piezoelectric elements after electrical excitation) close to the transducer surface that can obscure structures close to the catheter(405). This problem can be reduced to some degree by the application of a digital subtraction algorithm that differentially removes the ring down echoes. This is not a problem with rotational catheters as the transducer surface is separated by sufficient distance from the lumen for the ring down artefact to occur within the catheter space. Rotational catheters have two specific artefacts not present with the phased array design; firstly the guidewire is within the ultrasound field of view creating an arc of acoustic shadowing that obscures some of the lumen and vessel wall and secondly variations in rotation speed due to uneven drag by frictional forces on the drive cable causes a specific type of distorted image termed “non-uniform rotational distortion”(405).

Imaging can be achieved by a manual pullback, with the operator pulling the catheter back along the wire at a steady pace, or by means of a mechanical pullback system. Manual pullback allows the operator to concentrate on segments of interest as pullback can be paused as required. The increased likelihood of variable pullback speed limits its

use for quantitative analysis. Mechanical pullback allows the production of uniform, reproducible imaging and the acquisition of accurate length and volumetric information for quantitative analysis and is the standard method for IVUS imaging in coronary arteries research(25, 231). A limitation of motorized pullback is that the maximum practical pullback length available is 100mm. This is usually sufficient in the coronary arteries but limits the lesions that can be imaged in the peripheral arteries(11). Manual pullback is commonly used in peripheral studies to allow the inclusion of longer lesions (12, 14, 68, 149, 150, 410). The axial images can be “stacked” used to produce a longitudinal image. Problems with artefacts generated by catheter movement during the cardiac cycle can make interpretation difficult and quantitative analysis of this format is not recommended (25).

A2.3 Newer developments in IVUS imaging

The basic principles of operation of IVUS devices used today are essentially the same as the devices developed in the 1980’s. The improvements in IVUS technology since then have been incremental, primarily in improvements in image quality through improved signal processing and image storage, analysis tools that have enabled quicker and easier quantification, and the incorporation of IVUS into therapeutic devices such as CTO crossing devices, atherectomy and lumen re-entry devices.

Additional imaging features have been developed utilising other aspects of the ultrasound signal received by the IVUS transducer to provide additional information to interventionist. Virtual histology (VH) is a technology that analyses radiofrequency ultrasound backscatter signals to allow categorisation of tissue types with display using colour coding overlaid on the grey-scale IVUS image (411, 412). Although it is has been available for more than 15 years and has been extensively investigated in the coronary arteries there is a paucity of randomised controlled clinical trial evidence to support its use(412, 413) and there is disagreement about the validation of the VH tissue categories(414, 415).

More recently other tissue analysis methods have been developed. iMAP-IVUS utilising the same principles as VH but used a different colour coding map(416). IB-IVUS uses a different method of analysis to measure the power levels of backscatter signals to differentiate tissue types which, again, are overlaid as a colour coded display(417). Neither of these techniques have been as extensively investigated as VH and, like VH, their clinical role is unclear.

Although the use of VH has been reported in the peripheral arteries(11, 21, 418, 419) it

has not been validated for these vessels(409) and is limited by a maximum field of view of 10mm that, due to the propensity of the catheter to lie eccentrically within the lumen, effectively excludes its use in arteries with an EEM of >5mm(11).

Colour mapping of flow has also been developed for assisting the interventionist to differentiating areas of flow(419). Termed “chromoflo”, this method uses signal tracking software to detect changes in signal to differentiate between moving and static structures(420). It is unable to quantify flow velocity and has limited depth of penetration limiting its use in larger vessels(419, 420). The potential benefits of this technology include differentiation of patent lumen and echolucent plaque, identification of small branching arteries and delineation of plaque ulceration(419). Although there are anecdotal reports of its potential value in optimising endovascular treatment the peripheral arteries(419, 420), there is a lack of evidence regarding the use of this technology.

APPENDIX 3 IVUS IMAGING PULLBACK TECHNIQUES

The Boston Scientific Atlantis IVUS catheter uses a single fixed focus 40MHz ultrasound transducer rotating at 1800 rpm with a fixed frame rate of 30 frames/second and a maximum diameter field of view of 15mm. Mechanical pullback is performed using a mechanised sled that pulls the transducer back within the catheter at a rate of 0.5mm/second for a maximum length of 100 mm. The maximum length for a single pullback using this method is 100 mm. This pullback takes 3 minutes 20 seconds to be completed and produces a file of approximately 6000 cross-sectional images.

The Volcano system Eagle Eye and Visions PV018 catheters both use an array of 64 20MHz transducer elements arranged circumferentially around the catheter. The frame rate is variable on these catheters and the maximum frame rate (30 frames/second for the Eagle Eye and 24 frames/second for the PV018) was used in all cases. The maximum diameter field of view was 20 mm for the Eagle Eye and 24mm for the PV018 catheter. Mechanised pullback for these catheters is achieved by the use of a mechanised sled that pulls the entire catheter back though the vessel over the guidewire for maximum distance of 130mm. A pullback speed of 1.0 mm/second was used for all cases using the Volcano mechanical pullback, resulting in pullback times of 2 minute 10 seconds for a pullback of 130mm and files of approximately 3120 cross-sectional images.

Mechanical pullback offers the potential to acquire fully quantitative data when using the Atlantis catheter as the pullback is within the catheter itself and provides a highly uniform rate of pullback. Mechanical pullback with the Eagle Eye or PV018 catheters is subject to problems of non-uniform rates of pullback. This non-uniformity is due to friction between the catheter and vessel wall slowing or momentarily halting the progress of the catheter and to slack in the system resulting in the sled pulling the end of the catheter, outside the body, back but the tip of the catheter, inside the body, not actually moving. This non-uniformity of pullback results in data from this type of automated pullback being less reliable. The problem of slack in the system means that the practical pullback length of this system is more like 100mm than the maximum specification of 130mm

Multiple pullbacks were required when using the mechanical method for lesions greater than 100mm in length. These could be very time-consuming with a 30cm length of vessel requiring three separate pullbacks taking as much as 15 minutes due to the time taken to acquire three pullbacks and the time taken for set-up and resetting of the pullback sled between pullbacks. Imaging prior and after treatment could therefore add 30 minutes to

the procedure.

Manual pullback was an available option with the Volcano system and provided a means of imaging longer vessels without significantly increasing procedure times. This method involved the surgeon withdrawing the catheter over the wire at a steady rate. The surgeons already had extensive experience with endovenous ablation treatment, a technique that requires the ablation device to be manually pulled back through the vein at a slow and uniform speed for effective treatment. This experience was directly applied to IVUS pullback with the result that a steady pace of pullback was reliably achieved. Pullback was performed under continuous fluoroscopic control to enable constant identification of the catheter position within the artery. The transducer location was identified in relation to the radio-opaque ruler. Bookmarks were recorded using the s5 system's control functions at the start and end points of the pullback and every 2 cm to enable rapid location of image frames during image review. Bookmarking of bony landmarks (such as crossing the femoral cortex and the knee joint) and branching vessel fiduciary points was also performed to assist with verification of the position of image frames within the artery.

This method enabled much quicker image acquisition and more rapid feedback to the surgeon of quantitative and qualitative data required for treatment decision-making. Typically, manual pullback took about three minutes for imaging of a 30 cm lesion to be acquired. This compared very favourable with 15 minutes for the equivalent distance using mechanical pullback. While the manual pullback method had a lower density of frames/mm compared to the mechanical method, it still enabled a frame density of 14-18 frames/mm to be obtained for a 30 cm length during a 3 minute pullback acquisition. Feedback from the surgeons indicated that image quality was not noticeably affected in comparison with automated pullback and was sufficient for acquisition of diameter and length measurements and assessment of qualitative findings.

APPENDIX 4 QVA CALIBRATION

As described in Section 3.7.1, standard artery to table top distances at four sites within the femoropopliteal artery were generated to enable calibration of QVA software to allow vessel lumen measurements with minimal error due to magnification.

These were generated from a group of 20 patients prior to the start of the IVUS RCT. Rounded mean distances were obtained from these measurements. The accuracy of the quantification system when these distances were used was tested on a set of phantom tests and the potential error when the actual distance was different to the assumed distance was assessed.

Artery to table top distances for four sites in the femoropopliteal artery (proximal SFA just distal to the CFA birfucation, SFA distal at the proximal end of the adductor canal, popliteal artery P1 segment just distal to the adductor canal and popliteal P2/3 segment at the knee joint) were measured from the CTA scans, using the measurement tools on the hospital PACS system (Vue PACS version 11.4, Carestream Australia Pty, East Melbourne, Australia), of 20 patients (male:10, female:10), with a mean age of 71.4 years (SD=12.9) and a mean BMI of 27.4 (SD=4.8). The distances for the four sites in each leg in the 20 subjects are presented in Table A4.1.

Table A4.1 Table to artery distance in 20 cases measured from pre-procedure CT angiograms

ID number	Proximal SFA (cm)		Distal SFA (cm)		Popliteal P1 (cm)		Popliteal knee joint (cm)		Gender	Age	BMI
	R	L	R	L	R	L	R	L	1=male 2=female	years	
1	18.0	18.0	11.0	11.0	8.5	8.5	6.5	6.0	1	**67**	27.8
2	17.0	16.0	11.0	12.0	9.0	10.0	5.5	7.0	2	**89**	31.2
3	14.5	14.0	9.0	8.5	9.0	7.0	5.5	4.0	1	**95**	22.0
4	16.0	15.5	9.5	9.5	8.5	6.0	6.0	3.5	1	**58**	23.8
5	16.0	16.0	10.0	9.5	8.5	7.5	6.5	5.5	1	**85**	26.7
6	18.0	17.5	9.5	9.5	7.0	7.5	4.5	4.5	1	**62**	29.4
7	16.0	15.5	10.5	10.0	7.0	6.5	4.0	3.5	2	**59**	29.2
8	16.0	16.5	11.0	10.5	7.5	6.0	4.5	4.5	1	**84**	31.6
9	15.5	16.0	9.5	9.5	6.0	6.0	3.5	3.5	2	**66**	19.8
10	15.0	15.5	8.5	9.0	6.5	6.0	4.5	4.5	1	**65**	22.8
11	16.0	16.0	10.0	9.5	6.6	6.5	4.5	4.5	1	**48**	29.1
12	16.5	16.5	11.0	10.5	8.0	7.5	4.5	4.5	1	**79**	27.0
13	15.0	14.5	10.0	9.5	8.0	6.5	7.0	5.5	2	**81**	26.7
14	19.0	18.0	13.0	12.0	9.5	9.0	6.5	5.5	2	**71**	36.9
15	16.0	15.5	10.5	9.5	7.0	6.5	4.0	3.5	2	**80**	23.9
16	14.5	15.5	9.5	9.5	7.5	8.0	4.5	4.5	2	**86**	19.9
17	14.5	14.5	9.5	9.0	7.0	6.5	3.5	3.0	2	**69**	26.5
18	15.5	16.0	10.0	11.0	7.0	8.0	4.5	5.0	2	**52**	26.0
19	19.0	18.0	13.0	13.0	9.0	9.5	5.5	5.5	1	**64**	37.7
20	14.5	14.5	9.0	8.5	6.5	6.5	4.0	3.5	2	**67**	29.1

The mean distance and variance statistics for each site were calculated (Table A4.2). These results were rounded to the nearest half centimetre to simplify the phantom testing process (Table A4.3).

Table A4.2 Mean, standard deviation, minimum, maximum and ±2SD artery to table top distances for each of the four sites in the femoropopliteal arteries

n=40	artery to table top proximal SFA (cm)	artery to table top distal SFA (cm)	artery to table top popliteal artery P1 segment (cm)	artery to table top popliteal artery at knee joint (cm)
Mean	16.1	10.2	7.5	4.8
Std. Deviation	1.3	1.2	1.1	1.1
Maximum distance	19.0	13.0	10.0	7.0
Minimum distance	14.0	8.5	6.0	3.0
+ 2SD	18.6	12.9	9.7	7.2
- 2SD	13.4	8.1	5.3	2.8

Table A4.1 Rounded mean and ±2SD distances used for phantom calibration testing

	Rounded artery to table top proximal SFA (cm)	Rounded artery to table top distal SFA (cm)	Rounded artery to table top popliteal artery P1 segment (cm)	Rounded artery to table top popliteal artery at knee joint (cm)
Mean	16.0	10.0	7.5	5.0
+2SD	18.5	13.0	10	7.0
-2SD	13.5	8.0	5.5	3.0

A phantom calibration test was undertaken using an X-ray calibration device (YoyantMark, Brainlab AG, Kapellenstraße 12 85622 Feldkirchen, Germany) (Figure A4.1) to test the accuracy of using table top to artery distances to calibrate the QVA software and to calculate the potential error when the actual distance differed from the assumed distance. This phantom is an orthopaedic calibration device and consisted of a metal sphere on an adjustable arm to enable it to be fixed at a specified distance from the table top. Product specifications state that this ball was 25.4mm in diameter and this was confirmed using a precision Vernier calliper precise to 0.01mm (Figure A4.1).

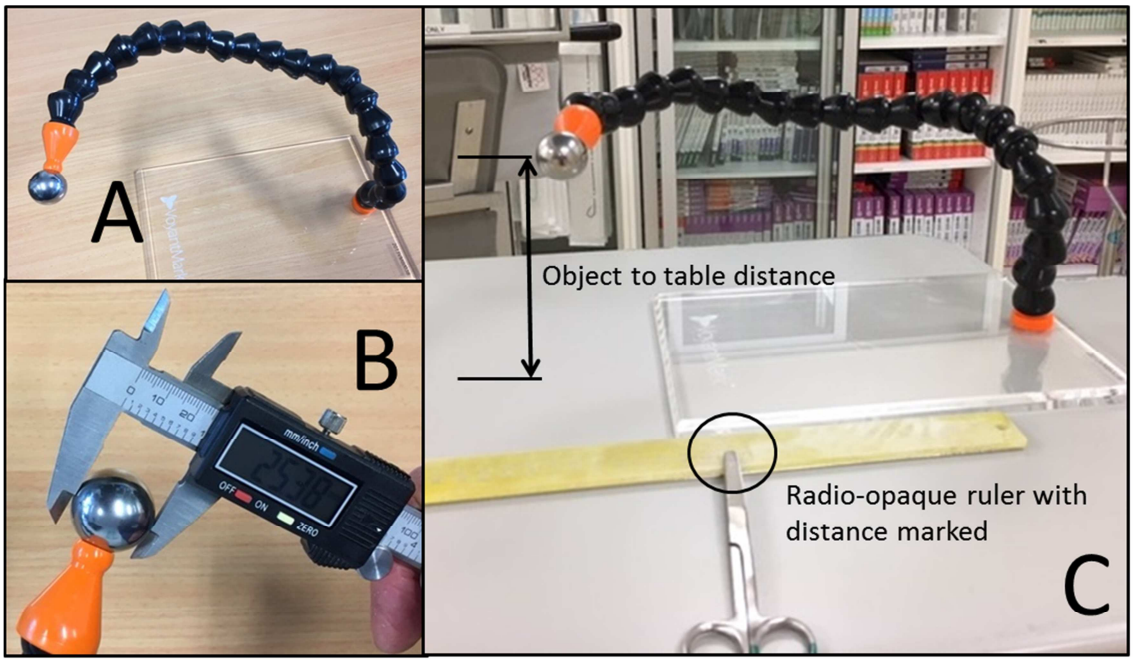

Figure A4.1 A. YoyantMark calibration phantom, B. confirmation of dimension of phantom object, C. Arrangement of phantom device and radio-opaque ruler on angiographic system table top

Radiographs were obtained using the angiography suite machine with the test phantom positioned at various distance from the table top (Figure A4.1). Three radiographs were obtained at each site in the femoropopliteal artery, at the mean object to table top distance and at a distance equal to ±2SD from the mean (see Table A4.3). A radio-opaque ruler with a marker was used to identify the object to table top distance used for each radiograph (Figure A4.2). The rounded mean artery to table top distance for each site (e.g.16cm for the proximal SFA) was then inputted into the quantification software and four diameter measurements across the calibration phantom were obtained (Figure A4.2) for each image.

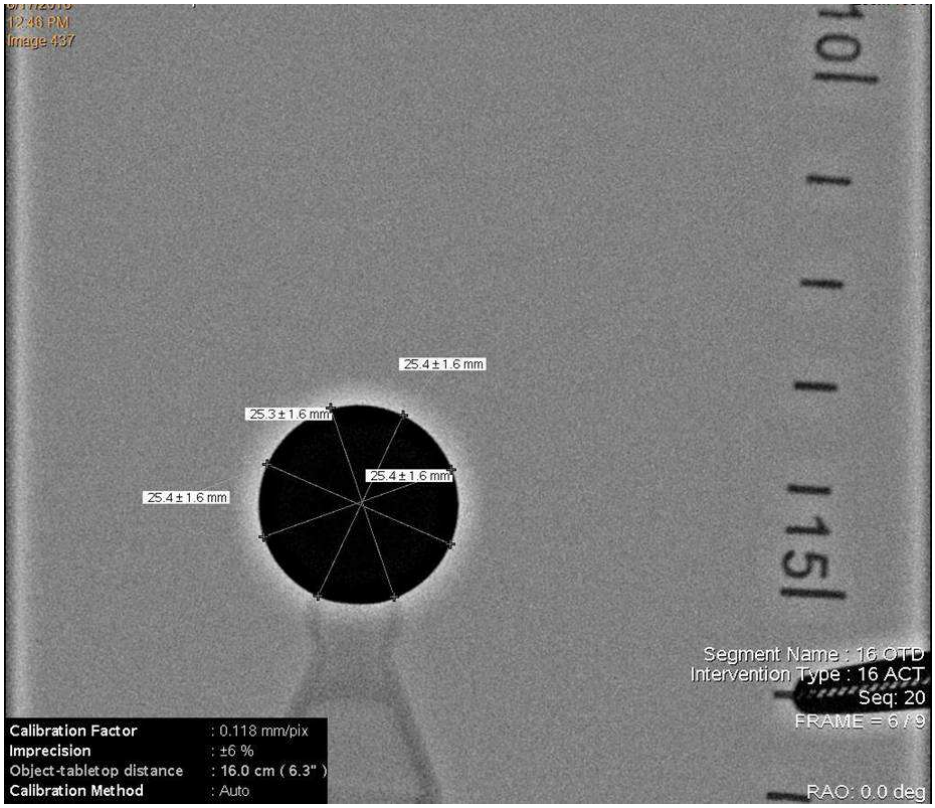

Figure A4.0.1 Radiograph of the phantom positioned at 16 cm above the table top with four diameter measurements obtained with the quantification software calibrated to an object to table top distance of 16cm

The mean of four diameters were calculated and this was compared to the known diameter of the phantom (25.4mm). The absolute difference between the actual and electronically measured diameter was calculated and represented the absolute error of the calibration. The absolute error of the calibration was then obtained for radiographs obtained with the test object at the 2SD above and below the mean distances with the software calibrated for the rounded mean distance. The absolute error was then divided by the actual diameter to give the percentage error for each site that could be expected depending on the inputted standard object to table distance. An estimate of the actual error in lumen measurements for the standard object to table distance at each site was then calculated by multiplying a typical lumen diameter (6mm lumen in the SFA and 5mm lumen in the popliteal artery) by each of the three percentage errors(mean, +2SD and -2SD) for the site. The potential error for these lumens was therefore calculated for a variation in the actual distance of +/-2SD from the assumed object to table distance (Table A4.4). These calculations confirmed that the potential actual error in lumen measurement for typical vessel lumen diameters when standardised object to table to distances were used was </= to 0.2mm.

Table A4.2 Mean phantom diameter measurements, absolute difference between the actual and mean measured phantom diameters, percentage difference between actual and measured distances in relation to actual lumen diameters

	Object to table top distance (cm)	Actual distance (cm)	Actual phantom diameter (mm)	Mean measured phantom diameter (mm)	Absolute error in phantom diameter (mm)	% difference in measurement	Actual vessel lumen diameter (mm)	Measured lumen diameter (mm)	Error in vessel measurement (mm)
+2SD	16	18.5	25.4	24.83	0.57	2.3	6	5.9	0.1
mean	16	16	25.4	25.38	0.02	0.1	6	6.0	0
-2SD	16	13.5	25.4	26.18	-0.78	-3.1	6	6.2	0.2
+2SD	10.5	13	25.4	24.35	1.05	4.1	6	5.8	0.2
mean	10.5	10.5	25.4	25.43	-0.02	-0.1	6	6.0	0
-2SD	10.5	8	25.4	26.13	-0.73	-2.9	6	6.2	0.2
+2SD	7.5	10	25.4	24.48	0.92	3.6	5	4.8	0.2
mean	7.5	7.5	25.4	25.38	0.03	0.1	5	5.0	0
-2SD	7.5	5	25.4	26.40	-1.00	-3.9	5	5.2	0.2
+2SD	5	7	25.4	24.48	0.92	3.6	5	4.8	0.2
mean	5	5	25.4	25.33	0.07	0.3	5	5.0	0
-2SD	5	3	25.4	26.23	-0.83	-3.2	5	5.2	0.2

APPENDIX 5 ADDITIONAL RESULTS FOR PERFORMANCE OF CALCIUM SCORING SYSTEMS

Table A5.1 Patient and lesion characteristics of sample population

Patient, lesion and treatment characteristics	n=60
Mean age, years (SD)	74.5 (9.5)
Gender - male	44 (73.3%)
Mean BMI, kg/m^2 (SD)	29.8 (4.9)
Smoking status	
Never smoked	14 (23.3%)
Current or previous smoker	46 (76.7%)
DM	21 (35.0%)
IHD	23 (38.3%)
HT	52 (86.7%)
Hyperlipidaemia	44 (73.3%)
Renal insufficiency (<60ml/min) (SD)	34 (56.7%)
Rutherford classification 3	36 (60.0%)
Rutherford classification 4&5	24 (40.0%)
TASC 1&2	33 (55.0%)
TASC 3&4	27 (45.0%)
Lesion location	
SFA	23 (38.3%)
SFA/Popliteal	26 (43.3%)
Popliteal	11 (18.4%)
Lesion type	
Stenosis	33 (55.0%)
Occlusion	18 (30.0%)
Restenosis	9 (15%)
Median treatment length, mm (IQR)	142.5 (217.5)

Table A5.2 Comparison of angiographic vessel parameters between two raters

	Rater 1 (n=60)	Rater 2 (n=60)	Significance
Lesion length (mm)	130 (163)	120 (184)	0.931*
Calcium present	36	40	0.001†
Calcium length (mm)	25 (123)	27.5 (63)	0.753*
Calcium length ≥ 50% lesion length	26	20	<0.001‡
Bilateral or 3-4 quadrant calcium	18	20	<0.002‡

Median (IQR), *Mann Whitney U test, †Fishers exact test, ‡Chi-square test

Table A5.3 Calcium scores according to the DEFINITIVE Ca++ scoring systems by two raters

		Rater 2			
		None/mild	Moderate	Severe	Total
Rater 1	None/mild	14	3	7	24
	Moderate	6	4	8	18
	Severe	0	3	15	18
	Total	20	10	30	60

Table A5.4 Calcium scores according to the PACSS scoring systems by two raters

		Rater 2					
		None	1	2	3	4	Total
Rater 1	No calcium	14	3	0	4	3	24
	1	6	1	1	1	0	9
	2	0	1	1	1	6	9
	3	0	0	0	2	0	2
	4	0	2	1	4	10	16
	Total	20	7	3	11	19	60

Table A5.5 Calcium scores according to the PARC scoring systems by two raters

		Rater 2					
		None	Focal	Mild	Moderate	Severe	Total
Rater 1	No calcium	14	2	1	7	0	24
	Focal	4	2	0	1	1	8
	Mild	2	1	1	2	4	10
	Moderate	0	0	0	2	0	2
	Severe	0	3	0	1	12	16
	Total	20	8	2	13	17	60

Table A5.6 Calcium scores according to the Fanelli scoring systems by two raters

		Rater 2								
		None	1a	1b	2a	2b	3b	4a	4b	Total
Rater 1	None	11	0	1	2	3	1	0	2	20
	1a	2	0	0	0	0	0	0	0	2
	1b	1	1	1	1	0	1	0	0	5
	2a	0	0	0	1	0	0	0	0	1
	2b	0	0	0	0	3	2	0	2	7
	3b	0	0	0	0	2	0	1	4	7
	4a	0	0	0	0	0	0	0	0	0
	4b	0	0	0	0	0	0	0	5	5
	Total	14	1	2	4	8	4	1	13	47