UNIVERSITA' DEGLI STUDI DI PARMA

DOTTORATO DI RICERCA in

Scienze Chirugiche e Microbiologia Applicata

CICLO XXX

Complex Infra-Popliteal Revascularisation in patients with Critical Limb Ischaemia: St. Thomas' Vascular Unit Experience

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Anni 2014 / 2017

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Statement of Originality and Acknowledgements

I declare that the research work in this thesis has been primarily carried out by me.

There are sections where other investigators have contributed towards the materialisation of this research work and these are outlined below:

- The database collection and analysis of patients undergoing distal bypass surgery has been performed by Mr Sanjay D. Patel, FRCS;

  Mr Patel and I are joint first-authors of the clinical work presented in Chapter 3.

  The results presented in Chapter 4 are based on the research project carried out mainly by my colleague Mr Patel; the decision to include this chapter is based on the intention to provide completeness to the topic of Complex Infra-Popliteal Revascularisation as presented in this thesis.

I would like to acknowledge and thank all the colleagues who contributed, in different ways, to this research project:

Tommaso Donati[1], Konstantinos Katsanos[2], Ioannis Paraskevopoulos[2], Justinas Silickas[1], Athanasios Diamantopoulos[2], Talia Lea[1], Judith S. L. Partridge[3], Jugdeep K. Dhesi[3] and Hany Zayed[1]

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[1] Guy's St.Thomas' NHS Foundation Trust; Department of Vascular Surgery

[2] Guy's St.Thomas' NHS Foundation Trust; Department of Radiology

[3] Guy's St.Thomas' NHS Foundation Trust; Department of Ageing and Health

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In addition, I declare that this thesis has not been submitted elsewhere for a higher degree.

Mr. Lukla Biasi
Consultant Vascular Surgeon

GUY'S and ST THOMAS' NHS Foundation Trust - ***The Vascular Unit***

The Vascular surgery department at St Thomas' Hospital is the hub site of the South East Vascular Network (SEVN) and has expertise in complex aortic, complex deep venous, lower limb and endovascular surgeries, receiving tertiary referrals from South East London, South West London, Kent and further afield.

The senior medical team consists of 12 consultant vascular surgeons, supported by a team of registrars, senior house officers and ward-based house officers. The department has two specialist vascular wards with a total of 51 beds (including 6 high-dependency beds), supported by clinical nurse specialists and dedicated vascular ward nurses.

Part of the tertiary vascular hub at St Thomas' includes the Hybrid operating facility which incorporates a specialist vascular operating theatre with imaging equipment to allow for intra-operative imaging and use of minimally invasive endovascular technique. The theatre is staffed by specialist cardiovascular theatre nurses and is located in East Wing, close to both the Intensive Care Units, and in the same wing as the vascular wards.

Endovascular techniques to re-vascularise an ischaemic leg are well established in vascular practice. They confer a good chance of technical success without the associated surgical stress of open bypass operations. St Thomas' Hospital has a large, well equipped Interventional Radiology Department with two dedicated Angio-Suites offering extensive expertise in the endovascular management of peripheral vascular disease in collaboration with the Department of Vascular Surgery. Both Peripheral Interventional Radiologists and dedicated Vascular

Surgeons (Lower Limb Team) independently run Angioplasty lists and collaboratively run Multi-Disciplinary Meetings (MDMs) weekly.

The state-of-the-art Hybrid theatre also offer the opportunity for the Lower Limb Team to undergo "hybrid", multilevel revascularisations both in elective and urgent settings.

St Thomas Hospital is also the regional referral centre of the South East London Diabetic Foot Network. As central unit, it runs a dedicated Diabetic Foot Service in Collaboration with other subspecialties including Diabetology, Infectious Diseases/Microbiology, Podiatry, and Interventional Radiology. The hospital is also responsible for running Foot Clinics in the smaller spoke hospitals. This forms an integrated network with the community podiatrists to allow for the assessment transfer and treatment of patients with Diabetic Foot disease that require revascularisation.

According to the National Vascular Registry, for the year 2015, St Thomas performed 380 lower limb endovascular procedures, 200 lower limb bypasses as well as 66 major lower limb amputations.

PERSONAL PROFILE

I am a qualified Vascular and Endovascular Surgeon with a dedicated commitment to the sub-specialty of Lower Limb Revascularisation.

I graduated with “distinguished honours" from the University of Bologna Medical School (Italy). Following a clinical and research fellowship at St. Georges’ Vascular Institute, I completed my specialist training at the University Hospital of Parma where I was appointed as Consultant Vascular Surgeon in 2009.

I moved to Guy’s and St.Thomas’ NHS Foundation Trust in 2014 where I was offered a Lower Limb Fellowship and I subspecialisized in complex open and endovascular lower limb procedures. I was appointed as a Consultant Vascular Surgeon at St Thomas’ in March 2016. I am an active member of the Lower Limb Team and Diabetic Foot Care Multi-Disciplinary-Team and I am running Vascular and Diabetic-Foot Clinics both at St Thomas’ and Tunbridge Wells Hospital.

Publications and Published Abstracts **(PhD programme 2014-2017)**

Peer reviewed scientific articles

1. **Biasi L,** Patel SD **,** Lea T, Donati T, Katsanos K., Partridge JSL., Dhesi J.K, Zayed H. *Complex Infra-Popliteal Revascularisation in Elderly patients with Critical Limb Ischaemia: Impact of Multidisciplinary Integrated Care on Mid-Term Outcome.* J Cardiovas Surg (Torino) 2016

2. Patel SD, **Biasi L***, Paraskevopoulos I, Silickas J, Lea T, Diamantopoulos A, Katsanos K, Zayed H. *Comparison of angioplasty and bypass surgery for critical limb ischaemia in patients with infrapopliteal peripheral artery disease*. Br JSurg. 2016 Sep 21

(* joint first author)

3. Clough RE, Zymvragoudakis VE, **Biasi L**, Taylor PR. *Usefulness of new imaging methods for assessment of type B aortic dissection.* Ann Cardiothorac Surg. 2014 May;3(3):314-8.

4. Geraghty J, **Biasi L**. *The use of larval debridement therapy in traumatic haematoma wounds.* J Wounds Uk; 10(2) supplement 2014

Published Abstracts and Conference Presentations

1. **L Biasi** *Endovascular Salvage of Threatened Bypass Grafts* (STARS Symposium 2017)

2. H. Abbas, P. Maghsoudlou, S. Kotecha, L. Mihaila, **L. Biasi**, T. Donati, M. Sallam, H. Zayed, S. Patel; London/UK *Factors predicting outcome following catheter-directed thrombolysis in lower limb arterial occlusion* (CIRSE 2017)

3. **L Biasi**, S Patel, I Paraskevopoulos, J Silikas, T Lea, , A Diamantopoulos, KN Katsanos, H Zayed *Infrapopliteal bypass versus angioplasty in patients with critical limb ischaemia compared using Propensity Score analysis* (The Vascular Societies 2016)

4. **L Biasi**, S Patel, I Paraskevopoulos, C Gordon, C Adkin, T Lea, T Donati, A Diamantopoulos, KN Katsanos, H Zayed *Predictors of clinical outcome following endovascular treatment of infrapopliteal disease in patients with critical limb ischaemia* (CIRSE 2016)

5. **L Biasi** , SD Patel, T Lea, T Donati, A Diamantopoulos, K Katsanos, J Partridge, J Dhesi, H Zayed *Complex Infra-Popliteal Revascularisation In Octogenarians And Nonagenarians With Critical Limb Ischaemia: Impact Of Multidisciplinary Integrated Care On Mid-Term Outcome* (ESVS 2016)

6. S D Patel, J Silickas, **L Biasi**, T Donati, T Lea, K Katsanos, N Patel, S Thomas, H Zayed. *Perioperative blood glucose levels influence outcome after infrainguinal bypass and endovascular therapy* (ESVS 2016)

7. SD Patel, **L Biasi**, I Paraskevopoulos MD , J Silickas, T Lea, A Diamantopoulos, K Katsanos, H Zayed. *Infra-popliteal bypass versus angioplasty in patients with critical limb ischaemia compared using Propensity Score analysis* (CIRSE 2016 – Poster)

8. L Biasi *Predictors of Clinical Outcomes following Tibial Endovascular Procedures in CLI* (STARS Symposium 2016)

9. **L Biasi**, S Patel, T Lea, L Newton, T Donati, K Katsanos, H Zayed. *Predictors of Outcome following Crural Endovascular Treatment in CLI* (British Journal of Surgery - The Vascular Societies, Annual Meeting 2015; Bournemouth – 13-15 November)

10. **L Biasi**, S Patel, V Zymvragoudakis, A Patel, T Lea, I Paraskevopoulos, L Newton, T Donati, K Katsanos, H Zayed. *Predictors of Mid-term Clinical Outcome following Endovascular Treatment of Infra-Popliteal disease in patients with Critical Limb Ischaemia* (ESVS 2015)

11. **L Biasi**, S Patel, S Padayachee, I Paraskevopoulos, L. Newton, T Donati, K. Katsanos, H. Zayed. *Midterm Outcomes of Salavage Angioplasty on Threatened Distal Bypass Grafts* (BSET, 2015 - Prize Session)

12. S Patel, **L Biasi**, V. Zymvragoudakis, T Lea, A Diamantoupolous, T Donati, K Katsanos, H Zayed. *Distal Bypass versus Angioplasty for Infra-popliteal disease in patients with Critical Limb Ischaemia* (ESVS 2015)

13. L Biasi *Aorto-Iliac Endoluminal Bypass: How I do it* (STARS Symposium 2015)

14. S Patel, **L Biasi**, V. Zymvragoudakis, T. Lea, A. Diamantoupolous, T. Donati, K. Katsanos, H. Zayed. *Atherosclerotic plaque analysis may help to predict outcome following lower limb endovascular intervention* (ESVS 2015)

15. T Donati, S Patel, **L Biasi**, T Lea, K Katsanos, H Zayed *Aorto-iliac Tasc C-D lesions: outcome of endovascular first approach* (British Journal of Surgery - The Vascular Societies, Annual Meeting 2015; Bournemouth – 13-15 November)

16. V. Zymvragoudakis, S D Patel, **L Biasi**, T Lea, T Donati, K Katsanos, H Zayed. *Mid-term outcome of hybrid revascularisation procedures for TASC C and D Aorto-iliac and Femoro-popliteal disease.* MEET 2015 Nice

17. V. Zymvragoudakis, S D Patel, **L Biasi**, T Lea, T Donati, K Katsanos, H Zayed *Atherosclerotic plaque analysis in the lower limb may help predict outcome following endovascular intervention.* MEET 2015 Nice. 1st Prize

THESIS OVERVIEW

Peripheral arterial disease (PAD) is the third leading cause of atherosclerotic cardiovascular morbidity, following coronary artery disease and stroke**.** In the 21st century, PAD has become a pandemic problem carrying significant healthcare, social and economic implications.

The prevalence of PAD is exponentially increasing, affecting over 200 million people worldwide (Nogren et al., *Inter-society consensus for the management of peripheral arterial disease (TASC II),* J Vasc Surg 207). Despite more than two-third of PAD patients being concentrated in low-middle income countries, over 61 million people are estimated to be affected by the disease in wealthy nations (40.5 million in Europe, 14.3 million in the Americas and 6.5 million in the western Pacific region); the incidence of PAD has increased globally by 23·5% in the last decade, with an estimated increased prevalence of up to 50% in the elderly population of high-income countries, due to the longer life expectancy (Fowkes et al. *Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis.* Lancet 2013).

Angiographic evidence of infra-popliteal disease, involving the tibial vessels, has been shown in approximately two third of the population with Critical Limb Ischaemia (CLI), requiring in most cases endovascular or surgical limb-salvage revascularisation (Bradbury et al. *Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: A survival prediction model to facilitate clinical decision making.* J Vas Surg 2010).

The management of distal (infra-popliteal) atheromatous disease remains a clinical and technical challenge, affecting a higher risk population burdened by more severe co-morbidities when compared to more proximal (femoro-popliteal) disease.

Despite many centres and guidelines recommending an endovascular-first strategy for infra-popliteal CLI, there is a paucity of scientific evidence to support the choice of treatment, with both bypass surgery and endovascular treatment showing relatively good outcomes. Two randomised controlled trials, the BASIL 3 and BEST-CLI, comparing the endovascular treatment versus bypass surgery, are still ongoing and their preliminary findings not being expected to be published anytime soon.

Surprisingly, an extensive analysis of the US Medicare population (Vogel et al. *Evaluating preventable adverse safety events after elective lower extremity procedures*. J Vasc Surg 2011) has shown an increased incidence of severe in-hospital complications after angioplasty, rather than after bypass surgery, in the elderly population. Furthermore, multiple randomised controlled trials (IDEAS, IN.PACT DEEP) have failed to prove any additional clinical benefit of the "drug coated" endovascular technology in the infra-popliteal segments.

The scope of this study was to conduct a retrospective analysis of a prospectively maintained database of consecutive CLI patients undergoing infra-popliteal endovascular and surgical revascularisation at a single institution, St Thomas' Hospital Vascular Unit.

This thesis is built on four sequential chapters to follow the outlined clinical research pathway:

Chapter 1 Analyses a large contemporary cohort of consecutive CLI patients undergoing infra-popliteal endovascular treatment (angioplasty) with a view of identifying the predictors of clinical outcome (Amputation Free Survival - AFS and Freedom from Major Adverse Limb Events - F-MALE).

Chapter 2 Provides a cohort subanalysis of the elderly patients (octogenarians and nonagenarians) comparing the clinical outcome following infrapopliteal

endovascular treatment versus bypass surgery. The importance of the peri-operative management (Comprehensive Geriatric Assessment - CGA) provided by the POPS team to improve survival and functional outcome has been emphasised.

Chapter 3 Compares the outcomes of bypass surgery and endovascular treatment in the whole cohort of CLI patients with infra-popliteal disease by using a Propensity Score Analysis. This statistical approach allows a strong level of evidence, correcting for selection bias and confounding factors. Awaiting for randomised controlled trials to publish their preliminary findings, statistical methods such as regression and propensity score models offer the best way to draw meaningful, evidence based conclusions to direct the treatment decision making.

Chapter 4 Examines the role of endovascular salvage angioplasty to maintain distal (infra-popliteal) bypass graft primary-assisted and secondary patency. The frequency of such interventions and the overall clinical outcomes (limb salvage and AFS) have been analysed.

CHAPTER 1.

Predictors of Clinical Outcome following Endovascular Treatment of Infra-Popliteal disease in patients with Critical Limb Ischaemia

Peripheral vascular disease is currently a global pandemic and is the third leading cause of cardiovascular morbidity. Despite that, there is still a paucity of scientific evidence on best management and clinical outcomes following infra-popliteal endovascular procedures in patients with Critical Limb Ischaemia (CLI). In this paper, we present a large contemporary series of consecutive CLI patients treated in a high volume centre. This study has shown normal eGFR, adjuvant inflow revascularisation as well as pre-procedural dual antiplatelet therapy as independent predictors of better mid-term amputation-free survival.

ABSTRACT

Objectives: The incidence of Critical Limb Ischaemia (CLI) is steadily rising among our aging population. This study sought to identify the predictors of clinical outcome in a large cohort of consecutive patients undergoing infra-popliteal (IP) endovascular interventions.

Materials and Methods: A prospectively maintained database of consecutive patients undergoing percutaneous IP revascularisation for CLI (Rutherford4-6) in our Institution between February2012-January2014 was analysed. Patients' demographics, cardiovascular risk-factors, angiographic findings and follow-up results were examined. The primary end points were amputation-free-survival (AFS) and freedom from major-adverse-limb-events (F-MALE) at 1 and 2 years. Secondary endpoints were technical success, primary, assisted-primary, secondary patency, freedom from target-vessel-reintervention (F-TVR) and limb-salvage (LS) rates by Kaplan-Meier analysis.

Results: 393 IP target-vessels were successfully crossed in 201 limbs (mean age 73 years; male 69.8%; DM 64%). Median hospital-stay was 6 days with 30-day mortality of 2%. Median Duplex follow-up was 16months. AFS was 77% and 55%, F-MALE was 72% and 64% at 1 and 2years, respectively. Technical success *per-limb* was 94% while technical success *per-target-vessel* was 85.6%. Primary, assisted-primary and secondary patency rates were 67%, 72%, 76% at 1 year and 49%, 54%, 60% at 2years. F-TVR was 77% and 69% and LS was 95% and 89% at 1 and 2 years, respectively. Multivariate Cox Regression identified *post-procedural dual-antiplatelet-therapy (DAPT)* as independent predictor of AFS (P=.034) and MALE (P=.002). Younger *age* (P<.001) and normal *baseline eGFR* (P=.009) were significantly associated to better AFS.

***Conclusions**:* Endovascular treatment of IP disease is safe and effective in patients with CLI. AFS is significantly worse in elderly patients and those with low eGFR whereas post-procedural DAPT is a predictor of better AFS and F-MALE.

INTRODUCTION

The prevalence of Peripheral Arterial Disease (PAD) is exponentially increasing worldwide affecting over 200 million people according to contemporary global estimates;[1] epidemiological studies predict an incidence of approximately 500 to 1000 new cases of Critical Limb Ischaemia (CLI) per million every year in the European and North American population, despite risk factors modification.[2]

Multidisciplinary consensuses and evidence-based guidelines have provided recommendations on the management of CLI based on clinical presentation and anatomic level of disease. These recommendations highlighted increasing evidence to support endovascular therapy in patients with CLI and Infra-Popliteal (IP) disease where in-line flow to the foot can be re-established.[3,4]

In over 60% of the CLI population, angiography shows significant tibial disease[5] with multi-level or isolated tibial angioplasty accounting for more than a third of all infra-inguinal endovascular procedures.[6]

Despite the fact that these procedures remain technically challenging, recent systematic reviews and meta-analysis of randomized trials have shown endovascular treatment of IP disease in CLI patients to be feasible and relatively safe, with a success rate up to 96.2% and 1-year survival up to 87.5%. Nevertheless the clinical outcome is compromised by a significantly low patency leading to major amputation rates as high as 17.8% in the first year.[7-11]

Previous studies focused mainly on device and technique-dependent results and were confounded by several limitations such as data reporting inconsistency, population and treatment heterogeneity and publication bias.[12] The aim of this study is to identify predictors of midterm clinical outcome following percutaneous revascularisation of IP disease in a large, homogenous cohort of consecutive CLI patients.

MATERIALS AND METHODS

A retrospective analysis of a prospectively maintained database of consecutive CLI patients undergoing percutaneous IP revascularisation in our Institution between February 2012 and January 2014 has been performed. Patients' demographic, cardiovascular risk factors, angiographic findings and follow-up results (clinical and radiological) were examined.

The primary endpoints were estimated Amputation Free Survival (AFS) and Freedom from Major Adverse Limb Events (F-MALE) at 1 and 2 years. Secondary endpoints were technical success, primary, assisted-primary, secondary patency, Freedom from Target-Vessel-Reintervention (F-TVR) and Limb-Salvage (LS) rates.

Definitions

We defined the endovascular treatment of infrapopliteal disease as the attempted percutaneous revascularisation of the crural vessels distal to the trifurcation of the popliteal artery, with or without concomitant inflow disease.

At completion angiography, we differentiated *technical success per limb* defined as successful recanalisation of at least one tibial artery with straight in-line flow to the foot and residual stenosis <30%, from *technical success per target vessel* defined as immediate patency with residual stenosis <30% for each of the treated arteries.

Primary patency, assisted-primary patency, secondary patency and F-TVR were defined according to the published SVS reporting standards[13].

Methods

Inclusion criteria in the current study were: i) CLI (Rutherford 4-6), ii) anticipated life expectancy longer than 6 months, iii) de-novo IP atheromatous steno-occlusive lesions with

or without proximal inflow disease were considered for percutaneous revascularisation. Exclusion criteria were: i) acute limb ischaemia, ii) redo tibial angioplasty, iii) IP angioplasty distal to bypass performed in order to improve outflow, iiii) patients not having a minimum of 6 months clinical and/or radiological follow up.

Pre-procedural assessment comprised of clinical evaluation and surgical risk stratification; diagnostic imaging included Echo-Colour-Duplex scan, performed by experienced vascular scientists as a first line diagnostic modality and CT-Angiography (CTA) or MR-Angiography (MRA) as indicated. Images were discussed in a dedicated multidisciplinary meeting where endovascular revascularisation plans are formulated and agreed upon.

In absence of specific contraindications, all patients were commenced on Best Medical Therapy (BMT) at pre-assessment; our Institution's protocol includes starting dual antiplatelet therapy immediately after the procedure for a 3 to 6 months' time. Patients already on anticoagulation for a different medical condition were discharged on 75mg Aspirin in addition to their anticoagulant therapy.

Endovascular interventions were performed either in a dedicated angiography suite (Siemens Artris Zee dTa; Siemens AG Medical Solutions, Germany) or in hybrid theatre (Philips Allura Xper FD20, Eindhoven, The Netherlands) by consultant interventional radiologists or consultant vascular surgeons. Access was achieved by US guided antegrade or retrograde puncture of the CFA depending on the target lesion and the planned strategy. Visipaque™ -iodixanol- was mainly utilized as isosmolar iodinated contrast medium. Prior to lesion crossing, a bolus of i.v. heparin (100 IU/Kg) was administered and Activated Clotting Time (ACT) regularly monitored throughout the procedure (target values of 200 to 300 seconds). The lesion was treated according to the operator's preference, preferentially intraluminally by

balloon angioplasty (Plain Old Balloon Angioplasty - POBA, Drug Coated Balloon - DCB) with stenting (Bare Metal Stenting - BMS, Drug Eluting Stenting - DES) being considered as a bailout option in case of suboptimal results. All images have been blindly reviewed by a specialist vascular surgeon and an interventional radiologist.

All discharged patients were enrolled in an outpatient surveillance program consisting of routine ultrasound duplex (within 6 weeks of the procedure, at 6 and 12 months then yearly thereafter) in an accredited vascular laboratory and clinical follow up (at 2 weeks and monthly thereafter) at our established multidisciplinary Foot Clinic. The time interval of surveillance was reduced in selected patients because of changes in the limb vascular status or to closely monitor an identified re-stenosis for progression.

Statistical Analysis

Variables are expressed as means ± standard deviation (SD) for parametrically distributed data and as median (range) for non-parametric test and continuous values, whereas categorical variables are presented as absolute values and percentages.

Primary and secondary endpoints were analysed using Kaplan Meier survival curves and the log rank test to look for differences. Cox regression model was used to identify independent factors associated with outcome variables. A (*P*) value of less than 0.05 was considered statistically significant. All analyses were carried out using SPSS 19 (IBM, New York, USA).

RESULTS

A total of 201 lower limbs were revascularised in 154 consecutive patients (mean age 73 years ±13). Patient demographics and baseline clinical characteristics are outlined in Table 1. Octogenarians and nonagenarians accounted for over one third of the study population (n= 56; 36.4%). The indication for treatment was tissue loss (Rutherford 5 and 6) in most of the cases (n= 153; 76.1%) with isolated rest pain accounting for only 23.9% (n=48) of the study cohort.

At pre-assessment, 67% of the patients (n=135/201) were on Best Medical Therapy - BMT (antiplatelet therapy and statin); the mean pre-operative Creatinine was 127μmol/L (SD +/- 114μmol/L) with a mean eGFR of 65 ml/min (SD +/-34ml/min).

393 IP target vessels were crossed in 201 limbs, with a median of 2 (1-3) vessels treated per limb (Anterior Tibial Artery: n= 119, 30%; Tibio-Peroneal Trunk: n= 100, 25%; Peroneal Artery: n= 87, 22%; Posterior Tibial Artery: n= 87, 22 %) (Table 2.). Complete foot arch revascularisation was successfully performed in 6.5% of the cases (n= 13/201).

Isolated tibial revascularisation was performed in 46% of the treated limbs (n=92) while adjuvant proximal revascularisation was needed in 54% of the cases (n=109); these adjuvant procedures consisted of iliac (n=5; 2%), ilio-femoral (n=2; 1%), femoral (n=36; 18%), femoro-popliteal (n=36; 18%) and popliteal (n=32; 16%) angioplasties.

At completion angiography, technical success per limb was 94.0% while technical success per target vessel was 85.6%.

Median hospital stay was 6 days (0-151) with a 30-day mortality of 2% (n=3).

Table 1. Patient demographics and their impact on Amputation Free Survival (Log Rank test)

Demographics	***N.***	***%***	***AFS***	***MALE***
Patients – (Limbs)	154 – (201)			
Age	73 (±13years)			
Male gender	132	66	*.72*	*.79*
Diabetes Mellitus (DM)	128	64	*.81*	*.46*
IHD	41	20	*.21*	*.92*
Current smoking	16	8	*.56*	*.63*
Arterial Hypertension	143	71	*.79*	*.81*
Hypercholesterolemia	75	37	*.72*	*.20*
Stroke / CVA	28	14	*.69*	*1.00*
Chronic kidney disease *(eGFR <60ml/min/1.73m^2)*	98	49	***.043***	*.18*
Dialysis	15	8	*.94*	*.69*
Statin	175	87	*.82*	*.48*
Warfarin	30	15	*.14*	*.55*
Beta Blockers	69	34	.16	*.72*
Pre-procedural DAPT	44	22.0	***.042***	.31
Post-procedural DAPT	111	55	***.008***	***.001***
Rutherford 4 *Rutherford 5* *Rutherford 6*	48 114 39	23 57 20	*.08*	*.37*
Adjuvant Inflow revascularisation	109	54	*.76*	*.58*
Multiple tibial angioplasty	127	63	*.54*	*.69*
Complete Pedal arch (pre) *Complete pedal arch (post)*	47 83	23 41	*.59* *.72*	*.77* *.33*
POBA *DCB* *BMS* *DES*	180 14 3 74	90 7 2 37	*.36* *.92* *NS* *.69*	*.35* *.26* *NS* *.22*

Table 2. Characteristics of tibial target vessels treated

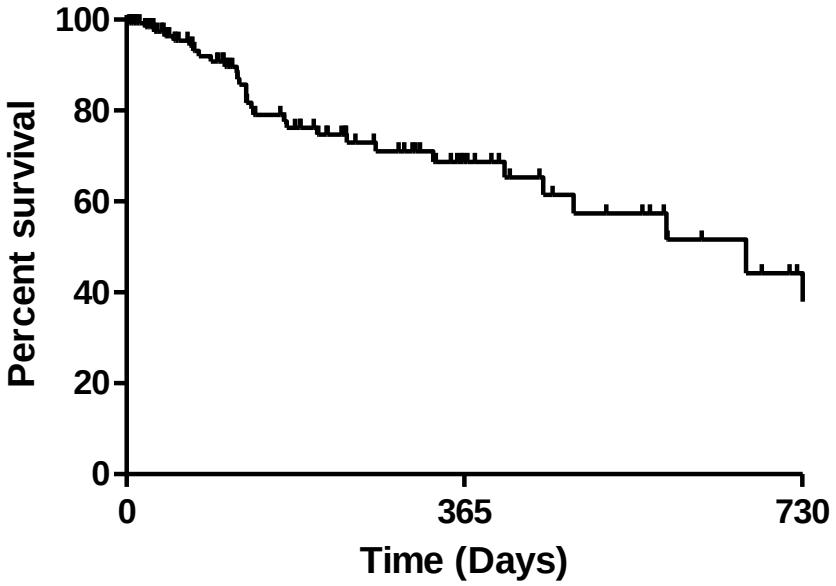
Tibial Target Vessel	N	%	Length (cm)
TPT	100	25	4.1(±1.3)
AT	119	30	22(±9.7)
PT	87	22	21(±9.8)
PeA	87	22	13.5(±8.4)

AFS by Kaplan Meier was 77% and 55% (Fig. 1) with F-MALE of 72% and 64%, at 1 and 2 years respectively.

Predicted primary, assisted-primary and secondary patency rates (per vessel) were 67%, 72% and 76% at 1 year and 49%, 54%, 60% at 2 years respectively; F-TVR was 77% and 69% and LS was 95% and 89% at 1 and 2 years, respectively.

On surveillance duplex scan - median follow up of 16 (6-56) months - 74 target-vessel occlusions (19%) were identified at a median of 10 (1-38) months from the primary intervention. Binary restenosis (>50%) rate was 12% at 1 year and 27% at 2 years. Indications for secondary procedures were non-healing ulcers or CLI with documented re-occlusion or binary re-stenosis. Reintervention procedures were performed on 50 limbs at a median of 6(0-39) months. Re-interventions consisted of redo-tibial angioplasty in 43 patients whereas 7 patients were deemed amenable to distal vein bypass. At the end of the follow up period 16 major limb amputations (n=16/201; 8%) and 70 deaths (n=70/201; 35%) have been documented. Overall survival by Kaplan Meier was 78% and 58% at 1 and 2 yrs respectively.

Fig. 1. Kaplan Meier Survival Curve showing Amputation Free Survival (AFS) after tibial angioplasty



Numbers at risk (SE of survival)

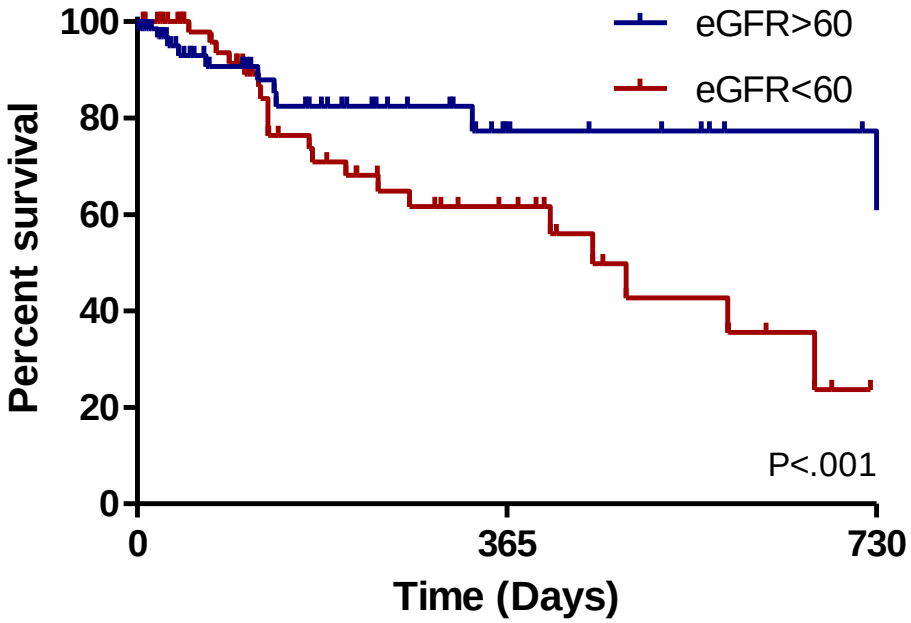
133	25(6)	4(10)

Predictors of Outcome

We carried out univariate and multivariate Cox regression analysis in order to look for independent factors which may predict AFS and F-MALE at 1 and 2 years.

In univariate analysis pre and post-procedural DAPT were significantly associated with better AFS (P= .042 and P= .008, respectively) (Fig.2), whereas chronic kidney disease - eGFR <60ml/min - correlated with worse AFS (P= .043) (Fig.3.). Post-procedural DAPT was the only significant factor associated with better F-MALE (P= .001) (Fig.4). All the other examined variables, including the features of the pedal arch at diagnostic and completion angiographies, the different materials and technique used (POBA, DCB, BMS, DES) were not associated with a better outcome.

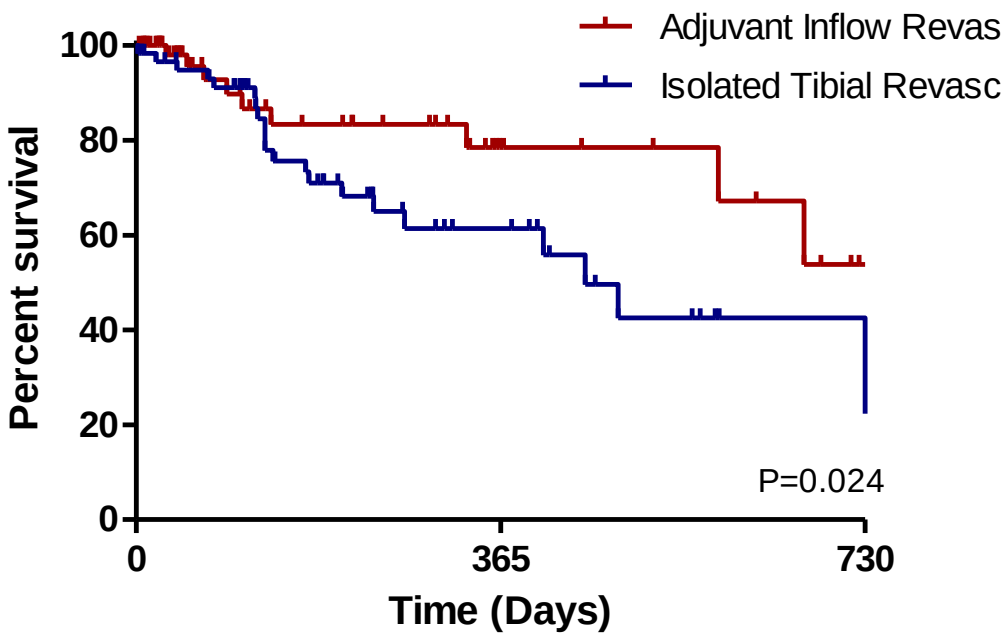
Fig. 2. AFS stratified according to eGFR (Log rank test)



Numbers at risk (SE of survival)

eGFR≥60	71	11(7)	4(7)
eGFR<60	62	15(8)	2(10)

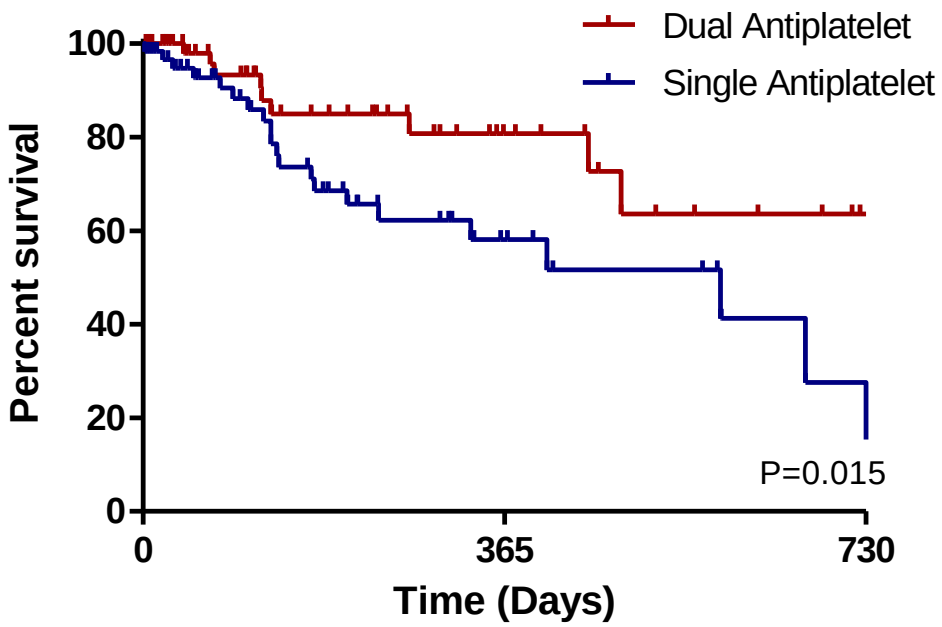
Fig. 3. AFS stratified according to the level of revascularisation (Log rank test)



Numbers at risk (SE of survival)

Adjuvant Inflow	69	12(8)	2(10)
Isolated Tibial	64	15(8)	2(10)

Fig. 4. AFS in patients taking dual compared with single anti-platelet agents (Log rank test)



Numbers at risk (SE of survival)

Dual Antiplatelet	70	14(7)	2(10)
Single Antiplatelet	63	12(8)	2(10)

Multivariate Cox Regression identified post-procedural dual-antiplatelet-therapy (DAPT) as independent predictor of both AFS (P=.034) and MALE (P= .002). Younger age (P< .001) and normal baseline eGFR (P= .009) were independent predictors of better AFS. (Table 3.)

Table 2. Multivariate Cox Regression Analysis showing factors affecting Amputation Free Survival and MALE

	Predictors of Outcome	Hazard Ratio (95% CI)		*P*
AFS	***Age***	**1.04**	**(1.02-1.06)**	***<.001***
	DM	1.16	(0.7-1.9)	.56
	eGFR	**0.99**	**(0.98-0.99)**	***.009***
	Pre-procedural DAPT	0.73	(0.39-1.37)	.32
	Post-procedural DAPT	**0.62**	**(0.4-0.97)**	**.034**
MALE	*Age*	1.00	(0.98-1.02)	*.88*
	eGFR	0.99	(0.98-1.00)	*.08*
	Post-procedural DAPT	0.44	(0.27-0.74)	***.002***

DISCUSSION

The incidence of PAD has increased globally by 23·5% in the last decade, with an estimated increased prevalence of up to 50% in the elderly population of high-income countries, due to the longer life expectancy.[14]

In the BASIL trial, nearly one-third of the CLI patients randomised in the endovascular arm required IP revascularisation; however, the number of patients potentially demanding distal endovascular treatment may have been underestimated by the exclusion of candidates with severe comorbidities or unsuitable distal anatomy precluding open surgery.[5]

CLI patients with IP atherosclerotic disease undoubtedly represent a higher risk population with impaired functional status and coexisting morbidities: the review of 13.258 hospitalized US Medicare patients undergoing tibioperoneal endovascular intervention reported higher comorbidity rates than the overall BASIL population.[15] In this context the TASC II consensus and more recently the Task Force on the Diagnosis and Treatment of Peripheral Artery Disease of the European Society of Cardiology (ESC) recommended an endovascular-first strategy in the IP segment for CLI patients.[2,16]

The present study reviewed our experience with endovascular treatment of IP steno-occlusive disease over a 23-month period. To date, this represents one of the largest series of consecutive CLI patients, recruited and treated in a relatively short time interval. We believed that analysing a contemporary cohort of patients would minimize the selection bias and the bias of continuous technological and pharmacological developments in the management of such condition. From a review of the published literature, only four single-centre case series in the last 10 years have investigated cohorts larger than 200 limbs undergoing IP

revascularisation.

The population analysed in our study was relatively younger and with less severe presentation when compared to the US Medicare population (median age of 73 years vs. 77 years; tissue loss in 77% of the cases vs. 89.5%), however burdened by a higher incidence of comorbidities such diabetes (67.5% vs. 46%) and chronic renal failure (46% vs 32%).[15]

In the present study, the successful restoration of straight-line-flow down to the foot (technical success per limb) was achieved in 94% of the cases with F-TVR rate of 77% at 1 year; this compares favourably to the pooled estimated results of a contemporary meta-analysis reporting immediate technical success and 1-year F-TVR rates of 92.3% and 73%, respectively.[17]

We adopted the composite endpoints of AFS and F-MALE as the appropriate clinical outcome measures of the present study. The Cox Regression analysis identified post-procedural dual antiplatelet therapy (DAPT) as an independent predictor of both AFS and F-MALE, highlighting the beneficial role of the dual-antiplatelet strategy in improving survival, limb salvage and minimizing the re-intervention rate.

In the literature, there is a lack of evidence-based guidelines for optimal antithrombotic treatment following peripheral endovascular intervention. Much of the supporting evidence for periprocedural antiplatelet therapy is extrapolated from the coronary intervention setting. However PAD and Coronary Artery Disease (CAD) are different manifestations of systemic atherosclerosis.

An updated Cochrane systematic review, investigating the effectiveness of antithrombotic drug in preventing restenosis or reocclusion after peripheral (iliac and femoro-popliteal

segments) endovascular treatment, showed a limited evidence on the advantage of antiplatelet drugs compared with placebo/control.[18]

However, the 2011 European Society for Vascular Surgery (ESVS) Guidelines for the management of critical limb ischemia (CLI) highlighted level 1b/grade B recommendations for the use of Aspirin or combined antiplatelet therapy to preserve patency following complex endovascular revascularization.[19]

A post-hoc analysis of the CHARISMA trial highlighted that patients with symptomatic PAD, may benefit from the combination of aspirin and Clopidogrel significantly reducing the risk of ischaemic events, over a 2-year time.[20] The MIRROR study, a single-centre, randomized, double-blind, placebo-controlled clinical trial, was the first to demonstrate the superiority of dual-antiplatelet therapy (DAPT) versus single-aspirin therapy in femoro-popliteal endovascular treatment reducing peri-interventional platelet activation and improving functional outcome.[21]

A more recently published metanalysis on 49 RCTs comparing different antiplatelet therapies in PAD patients have shown the favourable benefit of DAPT with Clopidogrel plus Aspirin in significantly reducing major adverse cardiovascular events. [22]

However no previous study has investigated the role of peri-procedural DAPT in patients undergoing distal, IP endovascular interventions. The present investigation showed the benefit of post-procedural DAPT on both composite endpoints of AFS and MALE. Pre-procedural DAPT proved to be associated to better AFS at univariate analysis but lost significance at multivariate Cox regression analysis.

In the current study, younger age and normal baseline eGFR were significantly associated to better AFS. Demographic features, angiographic classification of the pedal arch, Rutherford

classification and other comorbidities had no prognostic clinical impact.

Chronic kidney disease has been previously identified as a negative predictor of mid and long term LS following IP angioplasty.[23] The USA Nationwide Inpatient Sample analysis have acknowledged renal failure to be associated with a two-fold increased incidence of complications and iatrogenic events leading to a poorer clinical outcome after elective lower extremity procedures [24]. Taylor at al. have also shown end-stage renal disease (ESRD) to be to an independent predictor of poor outcome in a cohort of 677 patients after lower extremity revascularization (OR 1.46) [25]. Our results support these findings. Interestingly, a correlation between CKD and low Clopidogrel responsiveness (or increased HCPR) has also been recognized.[26,27] This may lead to a significantly higher risk of cardiovascular death, major amputation and re-intervention events at 1 year following peripheral angioplasty or stenting.[28]

The crural vessels have peculiar anatomical and haemodynamic features due to the small calibre of the tibial arteries, the histological pattern, the extension of the atherosclerotic disease and the configuration of the run-off system.[29] The technological advancement of endovascular materials and techniques in the last decades has revolutionized the approach of IP steno-occlusive disease trying to overcome complications such as restenosis, thrombosis, elastic recoiling, and dissections. However clinical outcomes proved to be neither device nor technique dependent:[30,31] drug eluting technology, although reducing the risk of MALE compared to BMS implantation, does not have a significant impact on survival.[32] Moreover a recent metanalysis of RCTs reporting overall 1-year primary and secondary patency as high as 65.7% (P= .92) and 73.5% (P= .13), failed to prove both technical and clinical superiority (survival P= .49, limb salvage P= .27) of primary stenting over plain old balloon angioplasty in the treatment of IP lesions,.[7] These findings are in line with our study showing how the clinical endpoints are statistically independent of the catheter-based strategy adopted, with

comparable 1-year primary and secondary patency rates of 67% and 76%, respectively.

Our analysis has shown no favourable clinical outcomes (AFS and F-MALE) in patients who had adjuvant inflow revascularisation when compared to isolated tibial interventions. The effect of disease distribution on the outcomes of tibial interventions is controversial. Gray et al. have highlighted worse clinical prognosis (AFS, LS, overall survival, maintenance of ambulation and independent living status) after single-level tibial revascularization compared to multi-level interventions. [33] It has been suggested that, despite the less extensive disease, patients with isolated tibial disease are more likely to have a locally increased atherosclerotic burden, therefore less responsive to conventional endovascular treatment. Fernandez et al. have reported poorer limb salvage rates among the subgroup of patients who underwent isolated tibial interventions but comparable overall-mortality and re-intervention rates.[34]

Despite the encouraging low perioperative mortality and high limb salvage rates, the results of revascularisation are limited by the poor life expectancy of this high-risk group of CLI patients. We reported an overall survival rate of 58% at two-years; this goes in line with a recent multicentre analysis on nearly 1000 CLI patients undergoing endovascular therapy which reported an estimated 2-year life expectancy less than 50% in high risk patients, with age being the strongest prognostic factor and a nearly fourfold increased mortality in octo-nonagenarians.[35]

The present study has the limitation of being a single-centre, retrospective and non-randomized analysis. Therefore, to support our findings, there is a need for multicentre randomized control trials. However, we acknowledge this may be practically difficult to conduct.

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CHAPTER 2.

Complex Infra-Popliteal Revascularisation in Octogenarians and Nonagenarians with Critical Limb Ischaemia:

impact of multidisciplinary integrated care on mid-term outcome

This chapter analyses the outcomes following distal, infra-popliteal, angioplasty and bypass surgery in a large cohort of octogenarian and nonagenarian patients undergoing a multidisciplinary approach, involving comprehensive geriatric assessment. No previous study has analysed the clinical outcome following distal revascularisation in the elderly population with Critical Limb Ischaemia. We have also identified independent predictors of outcome following these procedures.

ABSTRACT

Objectives: The incidence of Critical Limb Ischaemia (CLI) is exponentially rising among our aging population. There is a paucity of scientific evidence on best management and clinical outcome of infra-popliteal (IP) revascularisation in elderly CLI patients.

Materials and Methods: A prospectively collected database was analysed to identify consecutive octogenarian and nonagenarian patients who underwent IP revascularisation (bypass or angioplasty) for CLI (Rutherford 4-6) in a single centre between 2010-2014. The primary end points were overall Amputation-Free-Survival (AFS) and Overall Survival (OS) at 1 and 2 years. Secondary endpoints were primary, assisted-primary, secondary patency and Limb-Salvage (LS) rates by Kaplan-Meier analysis. Univariate and multivariate analysis was performed to find factors predicting outcome.

Results: A total of 129 limbs in 120 patients were treated with IP bypass (n=42) and endovascular (n=87) revascularisation with a mean age of 85(±5) years. The overall primary patency, assisted-primary patency and secondary patency were 58%, 65% and 70%, respectively at 12 months and 34%, 48% and 59% at 24 months. Primary, assisted-primary and secondary patency analysed by treatment method (endovascular vs. bypass) was 54% vs. 52%, 61% vs. 70%, 69% vs. 75% at 1 year and 21% vs. 36%, 24% vs. 62%, 31% vs. 72% at 2 years. The overall AFS at 12 and 24 months was 62% and 46% respectively; AFS was 71%-68% in the bypass group and 53%-21% in the Endovascular group (P<0.001). LS was 89% at 12 months and 84% at 24 months, with no significant difference between the bypass and endovascular groups (P=0.24). The overall perioperative mortality rate was 2%. OS by Kaplan-Meier was 68% and 54% at 1 and 2 years respectively. Diabetes (P=.046) and low eGFR (P=.041) were predictors of worse AFS and OS, respectively.

Conclusions: IP revascularisation (either endovascular or surgical) is feasible and effective in octogenarians and nonagenarians with CLI. By adopting a patient-tailored approach, both revascularisation strategies have satisfactory technical and clinical outcomes in this high-risk group. Subgroup analysis suggests that bypass surgery may have better mid-term secondary patency and AFS rates.

INTRODUCTION

At the dawn of the 21st century, lower extremity Peripheral Artery Disease (PAD) is a global pandemic affecting over 200 million individuals worldwide and representing the third leading cause of cardiovascular morbidity, following coronary artery disease and stroke.[1] Relatively uncommon among younger people, the prevalence of PAD rises exponentially with age, affecting a significant proportion of the elderly population.[2]

The estimated annual incidence of Critical Limb Ischaemia (CLI), defined as advanced stage of PAD presenting with typical chronic ischaemic rest pain and/or tissue loss, ranges from 500 to 1000 new cases per 1 million population.[3,4] CLI in patients who are not candidates for revascularisation is associated with a mortality rate as high as 25% in the first year, with only half of the remaining patients still alive without a major amputation.[5]. Current recommendations from numerous consensus documents and multidisciplinary guidelines highlight the crucial role of surgical and endovascular revascularization to achieve Amputation-Free-Survival (AFS) as the ideal primary outcome in CLI patients.[3,6]

In addition to AFS, the mobility status of the salvaged limb and the maintaining of functional independence are equally important outcome measures in the frail elderly CLI population. Vogel et al. showed that the functional status following endovascular or surgical revascularisation in this high risk population is multifactorial beyond procedural strategy.[7]

CLI patients with infra-popliteal (IP) atherosclerotic disease undoubtedly represent a higher risk population with impaired functional status, coexisting morbidities, and poor outcomes.[8] Distal revascularisation may be required in more than a third of all infrainguinal procedures [9]

and as the proportion of elderly patients continues to rise, there is a need for evidence-based analysis of the surgical management of elderly CLI patients with IP disease.

The purpose of this study is to examine the benefit of IP revascularization in octogenarian and nonagenarian CLI patients in a contemporary, single-centre, cohort study and to identify predictors of midterm clinical outcome.

METHODS

A prospectively collected database was analysed to identify consecutive octogenarian and nonagenarian patients that underwent primary IP revascularisation for CLI (Rutherford 4-6) in a single centre between 2010-2014. Revascularisation strategy was stratified into bypass or angioplasty. Revascularisation was defined as infra-popliteal (IP) if the distal anastomosis (bypass) or target vessel recanalisation (endovascular) involved the anterior tibial (AT), tibio-peroneal trunk (TPT), peroneal artery (PeA), posterior tibial (PT), or dorsalis pedis (DP), with or without a concomitant inflow procedure. Patients' demographic, cardiovascular risk factors, angiographic findings, operative variables and follow-up results (clinical and radiological) were analysed to find factors predicting outcome. All patients gave informed consent, which included data collection. As per National Health Service Research and Ethics definitions (Institutional Review Board equivalent, http://www.nres.nhs.uk/) this study is not classified as research requiring formal ethics approval.

Peri-Operative Management

Pre and perioperative management is coordinated by the 'Proactive care of Older People undergoing Surgery' (POPS) team. The POPS team comprises consultant geriatricians, nurse specialists in older people, occupational therapists, physiotherapists and social workers. They provide an inpatient and outpatients service with the aim of proactively managing medical co-morbidities and geriatric syndromes (such as cognitive impairment, postoperative delirium and frailty) which have been shown to adversely impact postoperative outcomes and increase length of stay (LOS).[10,11] This is done by The Comprehensive Geriatric Assessment (CGA), which is an established approach that identifies medical, psychosocial and functional needs and optimises them by using a clearly defined plan for management and follow up.[12] CGA

has been shown to improve survival and function.[12] Postoperatively, the team reviews patients on the surgical wards providing direct intervention and staff education in early detection and treatment of medical complications, delirium, early mobilisation, pain management, bowel-bladder function, nutrition and discharge planning. Following discharge, the POPS team provided a follow-up therapy home visit in those with functional difficulties and outpatient clinic review in those with on-going medical problems. The care of patients on discharge is transferred to primary care. Primary care is provided with detailed information on when and how to seek specialist support from vascular, medical and/or geriatric medicine specialists working in their local areas. All patients are provided with a contact for a vascular clinical nurse specialist in case of need for advice. All patients receive a copy of the electronic discharge letter which details this information in written form.

Procedural Details

All patients with CLI and with anticipated life expectancy longer than 6 months were considered for revascularisation. Diagnostic imaging included duplex ultrasound, CT-Angiography (CTA) or MR-Angiography (MRA) as indicated. Images were discussed in a dedicated multidisciplinary meeting where the best revascularisation strategy was agreed upon, after careful consideration of patients' co-morbidities, availability of suitable venous conduit, anatomical distribution and extent of the disease. Patients without adequate autogenous veins were considered for primary endovascular treatment.

Technical details of the bypass procedure have been previously published.[13] Pre-operative duplex scanning was used to identify a venous conduit where possible, with the great saphenous vein (GSV) as the preferred conduit followed by the small saphenous vein (SSV) or arm veins (cephalic and basilic). Bypass grafts were tunnelled anatomically in a reversed

or non-reversed (with valvulotome) way as deemed appropriate depending on the size match between the vein and the inflow and outflow artery. Unfractionated heparin (100 IU/Kg) was given intravenously before vessel clamping and additional boluses administered to maintain the activated clotting time (ACT) between 200 to 300 seconds.

Endovascular interventions were performed either in a dedicated angiography suite or in hybrid theatre by consultant interventional radiologists or consultant vascular surgeons. Prior to lesion crossing, a bolus of i.v. heparin (100 IU/Kg) was administered and Activated Clotting Time (ACT) regularly monitored throughout the procedure (target values of 200 to 300 seconds). The lesion was treated according to the operator's preference, preferentially intraluminally by balloon angioplasty (Plain Old Balloon Angioplasty - POBA, Drug Coated Balloon - DCB) with stenting (Bare Metal Stenting - BMS, Drug Eluting Stenting - DES) being considered as a bailout option in case of suboptimal results.

All patients received dual antiplatelet therapy immediately after the procedure for 3 to 6 months'. Patients already on anticoagulation for a different medical condition were discharged on 75mg Aspirin in addition to their anticoagulant therapy.

All bypasses were enrolled in our duplex surveillance programme consisting of scans pre-discharge and 3, 6, 9 and 12 months post-procedure and yearly thereafter, if no intervention was necessary; all endovascular patients had surveillance duplex at 6 weeks, 6 months and as clinically indicated thereafter. Secondary re-do procedures (to achieve primary-assisted or secondary patency) would re-set the surveillance programme to the starting point.

Study end points and statistical analysis

The primary end points were overall Amputation-Free-Survival (AFS) and Overall Survival (OS) at 1 and 2 years. Secondary endpoints were primary, assisted-primary, secondary patency and Limb Salvage (LS) rates by Kaplan-Meier analysis and defined according to the published SVS reporting standards.[14] For the purpose of defining AFS, amputations above the ankle were considered major limb amputations. Technical success was defined as a less than 30% residual stenosis on completion angiogram, in the endovascular group and as intraoperative detection of triphasic CW Doppler signals on the target vessel, in the bypass group. Continuous variables are expressed as means ± standard deviation (SD) for parametrically distributed data and median (range) for non-parametric data, whereas categorical variables are presented as absolute values and percentages. The primary end points were compared using the log rank test and results expressed as Hazard Ratio (HR) with 95% Confidence Interval (CI). A P value of <0.05 was considered statistically significant. All analyses were carried out using GraphPad Prism 6 (GraphPad Software Inc., San Diego, California) and SPSS 22 (IBM, New York, USA).

RESULTS

A total of 129 limbs in 120 octogenarian and nonagenarian patients were treated with distal bypass (n=42) and endovascular revascularisation (n=87) with a mean age of 85(±5).

Patient demographics and cardiovascular risk factors are listed in Table I stratified by mode of intervention which shows that smoking (current or ex-smoker) was significantly more common in the bypass group (P<0.001), with no other significant differences. Indication for treatment was CLI Rutherford stage 4 (37%), stage 5 (57%) or stage 6 (6%).

Table 1. Patient demographic details stratified according to mode of revascularisation

Variables	Bypass	Endovascular	P value
Patients (Limbs)	41(42)	79 (87)	-
Age	85(±4)	85(±5)	.72
Male gender	28	*44*	*.09*
Diabetes Mellitus (DM)	19	*44*	*.35*
IHD	9	*16*	*.43*
Stroke/TIA	10	*11*	*.09*
Current smoking	15	*6*	*<0.001*
Hypertension	30	*59*	*.42*
Hypercholesterolemia	17	*29*	*.27*
Creatinine	113(±78)	*128(±101)*	*.41*
eGFR	62(±25)	*55(±28)*	*.18*
Aspirin	29	*56*	*.34*
Clopidogrel	10	*26*	*.42*
Statin	34	*74*	*.25*
Disease Severity			
Rutherford 4	16	*21*	*.13*
Rutherford 5	22	*52*	
Rutherford 6	4	*13*	

Target vessel for the bypass group was the AT (29%), PT (26%), PeA (24%), TPT (14%), and DP (7%) artery. No adjuvant proximal endovascular revascularisation was required prior to the bypass surgery. Venous conduit was the GSV in most cases (95%) except two limbs where the SSV and composite arm veins were used respectively. Vein grafts were tunnelled anatomically and placed reversed (48%) or non-reversed (52%) with a mean pre-operative diameter of 4(±1) mm. Technical success before leaving the operating table was 100%.

There were 169 infrapopliteal endovascular target vessels; a mean of 2 target vessels per patient were successfully crossed and treated. (Anterior Tibial Artery: n= 54, 32%; Tibio-Peroneal Trunk: n= 42, 25%; Posterior Tibial Artery: n= 37, 22%, Peroneal Artery: n= 36, 21%). Treatment modality included POBA (n=79, 91%), DCB (n=5, 6%), BMS (n=1, 1%) and DES (n=37, 43%). Isolated tibial endovascular revascularisation was performed in 47.1% of the treated limbs (n=41) while adjuvant proximal revascularisation was needed in 52.9% of the cases; these adjuvant procedures consisted of superficial femoral artery (n=6/46; 13.0%), femoro-popliteal artery (n=17; 37.0%) and popliteal artery (n=23; 50%) angioplasties. At completion angiography, technical success per target vessel was 86%, and technical success per limb (defined as achieving at least one open vessel to the foot) was 94.0%.

Primary patency, assisted primary patency and secondary patency for the whole group was 58%, 65% and 70% respectively at 12 months and 34%, 48% and 59% respectively at 24 months (Figure 1 A, B and C). Primary, assisted primary and secondary patency analysed by treatment method (endovascular vs. bypass) was 54% vs. 52%, 61% vs. 70%, 69% vs. 75% at 1 year and 21% vs. 36%, 24% vs. 62%, 31% vs. 72% at 2 years. There was no significant difference in primary patency between the bypass and endovascular group (P=.66), though

assisted primary (P=.008) and secondary patency (P=.017) were significantly better in the bypass group (Figure 1 A, B and C).

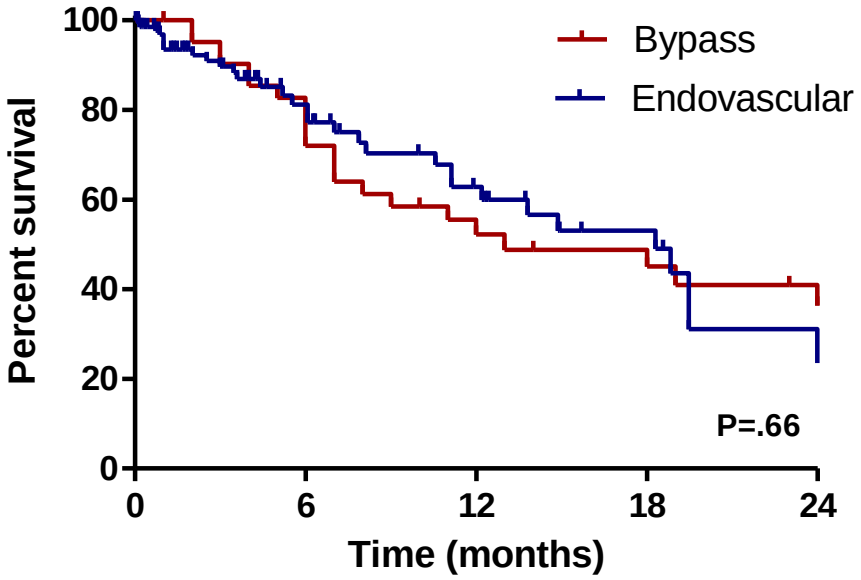
Within the bypass group, 15 (36%) grafts required secondary interventions to maintain patency at a mean of 10(±7) months from bypass. All secondary procedures were endovascular in the first instance with three grafts eventually requiring surgical intervention (two anastomotic revisions and one jump graft to an adjacent tibial vessel). A further 5 graft were treated for acute occlusion, 4 underwent successful thrombolysis and one required surgical thrombectomy.

The overall AFS was 62% at 12 months and 46% at 24 months, with a significantly better AFS in patients undergoing bypass (P<.001, Fig 2). There were 12 major limb amputations performed for Rutherford 4 (n=6) and Rutherford 5 and 6 (n=6) CLI at a median of 5(1-17) months from revascularisation.

The overall limb salvage (LS) rate was 89% at 12 months and 84% at 24 months, with no significant difference between the bypass and endovascular groups (P=0.24). There were two mortalities in the first 30 days (2%) which occurred in patients who had undergone endovascular revascularisation. The first death was secondary to myocardial infarction on day 30. The second death was secondary to cardiac arrest during a re-intervention for persistent symptoms of CLI. Both of these patients had been discharged from hospital following their index revascularisation procedure. Over the study period there were 42 deaths in the patient cohort at a mean of 12(±13) months. OS by Kaplan Meier was 68% and 54% at 1 and 2 years respectively.

Analysis of discharge destination showed that 79% of patients returned to independent or assisted living at home, 15% required further bed based rehabilitation, and only 6% were discharged to a nursing home.

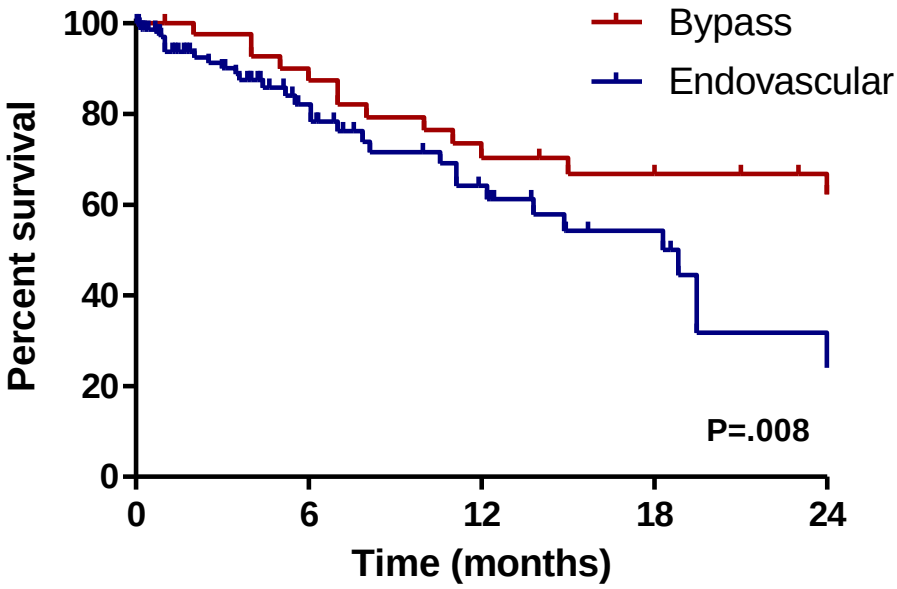
Fig 1. Kaplan Meier survival curves showing A. Primary Patency, B. Assisted Primary Patency and C. Secondary Patency stratified by mode of treatment (Log Rank Test)



A.

Numbers at risk (SE of survival)

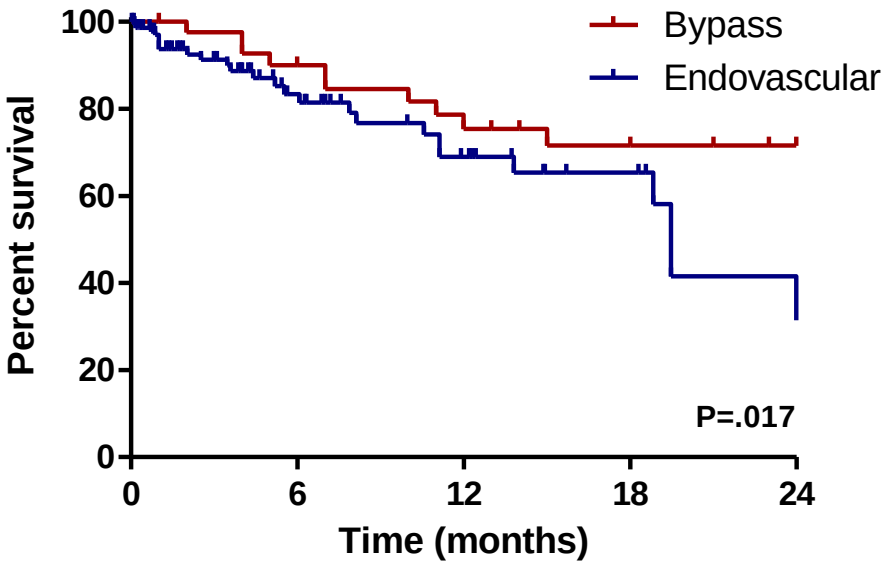
Bypass	42	17(8)	9(9)
Endovascular	169	25(7)	7(10)



B.

Numbers at risk (SE of survival)

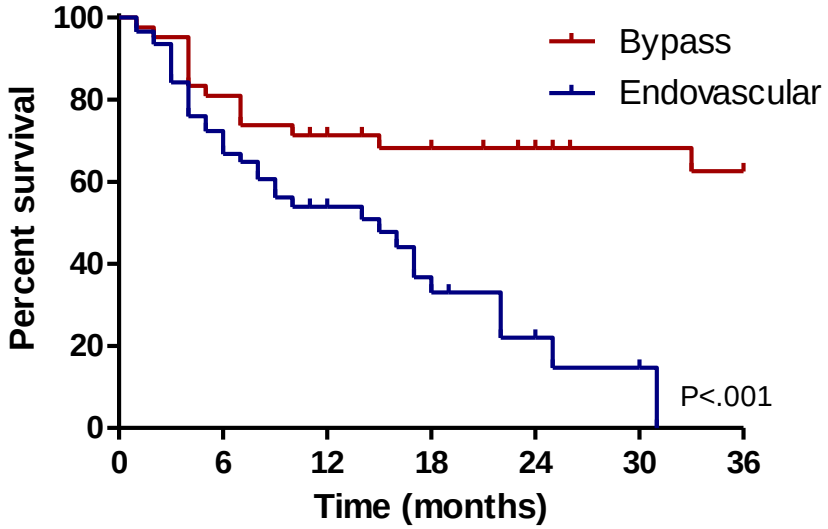
Bypass	42	23(8)	15(9)
Endovascular	169	25(6)	7(10)



C. Numbers at risk (SE of survival)

Bypass	42	24(7)	15(8)
Endovascular	169	26(6)	7(10)

Fig 2. Amputation free survival in patients undergoing infra-popliteal bypass and endovascular revascularisation (Log rank test)



Numbers at risk (SE of survival)

Bypass	42	26(7)	18(7)	11(9)
Endovascular	87	21(7)	4(8)	-

Predictors of Outcome

We carried out univariate and multivariate Cox regression analysis in order to look for independent factors which may predict AFS and overall survival (Table 2 and 3). In univariate analysis Diabetes (P=0.027 and P=0.041) and Endovascular revascularisation (P<0.001 and P<0.001) correlated significantly with worse AFS and overall survival respectively (Table 2). Cox regression analysis was performed to look for factors significantly associated with AFS and overall survival (Table 3), and included factors found to be significant in the univariate analysis as well as continuous variables such as age and eGFR. Diabetes (HR 0.58, 95% CI 0.32-1.0, P=.046) as well as Endovascular revascularisation (HR 0.33, 95% CI 0.16-0.65, P=.001) were the only independent factors predicting worse AFS. Factors independently associated with worse overall survival were low eGFR (HR 0.98, 95% CI 0.98-1, P=.041) and endovascular revascularisation (HR 0.15, 95% CI 0.06-0.38, P<.001). Age was not found to be an independent predictor within our cohort of elderly patients.

Table 2. Univariate analysis of factors affecting freedom from Major Adverse Limb Events (MALE), Amputation Free Survival (AFS) and overall Survival (Log Rank Test)

Variables	Freedom from MALE	AFS	Survival
Male gender	.74	*.47*	*.99*
Diabetes Mellitus (DM)	.17	*.025*	*.041*
IHD	.88	*.71*	*.90*
Stroke/TIA	.98	*.63*	*.62*
Current smoking	.10	*.072*	*.12*
Hypertension	.5	*.61*	*.24*
Hypercholesterolemia	.84	*.61*	*.39*
Aspirin	.11	*.97*	*.28*
Clopidogrel	.46	*.74*	*.72*
Dual antiplatelets	.83	*.72*	*.71*
Statin	.68	*.26*	*.51*
Rutherford 5+6	.056	*0.75*	*.69*
Endovascular Group	.86	*<0.001*	*<0.001*

Table 3. Cox regression analysis of factors predicting amputation free survival and overall survival (Diabetes Mellitus – DM, estimated Glomerular Filtration Rate –eGFR)

End point	Variable	Hazards Ration	95% CI	P Value
Amputation Free Survival	**DM**	0.58	0.32-1.0	**.046**
	eGFR	0.98	0.96-1.0	.096
	Endovascular Group	0.33	0.16-0.65	**.001**
Survival	DM	0.62	0.32-1.18	.15
	eGFR	0.98	0.98-1	**.041**
	Endovascular Group	0.15	0.06-0.38	**<.001**

DISCUSSION

The estimated age-specific prevalence of PAD in octogenarians and nonagenarians living in high-income countries is greater than 80%, with the rate of PAD increasing by over 50% in the population aged 80-84 years in the last decade only, despite risk factors modification. [1]

Life expectancy remains poor in CLI patients as shown by a metanalysis of contemporary prospective studies on patients diagnosed with CLI which has reported overall mortality rates of 7.5% at 1 year, 35.1% at 3 years and 46.2% at 5 years, regardless of the treatment strategy, with age and ischaemic heart disease being the only predictors of mid-late term mortality.[15] However, successful infrainguinal revascularisation in elderly CLI patients has proven to be effective, improving symptoms, quality of life and 1 year AFS rates when compared to conservative treatment.[16-18] Interestingly, previous studies showed better LS (19) and 1year survival rates[17] in octogenarians as compared to younger patients after revascularisation for CLI.

In BASIL trial, a UK multicentre RCT, IP arterial reconstruction accounted for 29.3% of all endovascular treatments and 43% of all bypass surgery.[9] According to a report from the Nationwide Inpatient Sample of the USA on 13.258 patients undergoing IP interventions, more than two fifths were 80 or more years old, with age being a significant risk factor of 30-day mortality.[8]

To our knowledge no previous study has specifically investigated the early and mid-term clinical outcome following IP revascularisation in octogenarians and nonagenarians with CLI.

In the current analysis perioperative mortality among octogenarians and nonagenarians following IP revascularisation within 30 days was 2%. This compares favourably to historic series of infrainguinal surgical revascularisations (including femoro-popliteal procedures) in elderly patients, reporting perioperative mortality rates as high as 15% [20]; a more recent European single-centre study, focusing on infrainguinal revascularisation in the same age group population, reported an overall perioperative mortality rate of 7.4% (9.5% after bypass surgery vs. 5.1% after angioplasty).[16]

The American College of Cardiology / American Heart Association guidelines on perioperative cardiovascular risk evaluation classify peripheral arterial reconstructive surgery as a high risk procedure.[21] Considering the advancement of catheter-based technology, it is arguable that the endovascular treatment in complex IP revascularisations on elderly, frail patients may potentially be considered the first line approach as it is minimal invasive with less cardiovascular stress and shorter hospital stay.[22-24] Single centre cohort studies seem to support this hypothesis reporting higher perioperative mortality rates (up to 20-fold increase) after surgical infrainguinal procedures in octogenarian patients.[16,17] On the contrary, Vogel et al.'s analysis on a total of 226.501 lower limb procedures (US Medicare population) demonstrated the increased likelihood of having in-hospital, life threatening complications after angioplasty rather than after open surgery, especially in patients older than 80 years.[25] European nationwide analysis has also shown the superiority of IP surgical reconstruction in achieving LS (P: 0.027) when compared to IP endovascular treatment (P: 0.332).[26] Of note, drug coated technology failed to prove any additional clinical benefit when compared to "Plain Old Balloon Angioplasty" (POBA).[27,28]

In our series the outcome in terms of patency, AFS and overall survival was significantly better in the bypass group compared to the endovascular group. However, it should be noted that the mode of revascularisation was decided based on MDM discussions rather than randomisation. As such, these results are subject to potential selection bias. There is a natural tendency to select fitter patients to undergo open surgery and this may be reflected in the better results in this group; on the other hand a direct cohort comparison showed no significant differences in comorbidities other that smoking that is more prevalent in the bypass group. We need to wait for the results of the ongoing BASIL 2 (http://www.isrctn.com/ISRCTN27728689) and BEST-CLI[29] trials in order to achieve level A evidence on the comparative benefit of bypass surgery versus best endovascular treatment in IP revascularization.

On these premises, we believe that complex IP revascularization procedures to be tailored on each patient according to his/her clinical and anatomical features and to be performed in high-volume centres with acceptable results both in endovascular and bypass surgery.

AFS rate at 1 year in our cohort of elderly patient was 62% which compares favourably to previous studies on CLI octogenarians treated with either infrainguinal angioplasty or bypass surgery showing AFS rate of 58%.[16,30] In our study, the Cox Regression analysis identified diabetes as independent predictor of AFS and eGFR as predictors of overall survival. The USA Nationwide Inpatient Sample analysis have acknowledged diabetes mellitus (OR 1.20) and renal failure (OR 2.31) to be associated to an increased incidence of complications and iatrogenic events (patient safety indicators - PSIs) after elective lower extremity procedures[25]; moreover the same authors reported chronic renal failure as a specific predictor of 30-day re hospitalization (OR 1.4) following IP interventions.[8] Taylor at al. have also shown end-stage

renal disease (ESRD) to be to an independent predictor of poor outcome in a cohort of 677 patients after lower extremity revascularization (OR 1.46).[31]

The low perioperative mortality rates and good post-procedural outcomes in the current study could be explained by the comprehensive geriatric assessment (CGA) for at-risk older patients undergoing elective surgery. A recent Cochrane meta-analysis of 22 trials of 10.315 hospitalised participants comparing CGA with standard care reported a significantly higher probability of being both alive and in their homes at 6 and 12 months ($P< 0.001$).[32] In our institution, the POPS team provides a pre-operative multidisciplinary, patient-centred, evidence-based CGA service with post-operative follow-through.[10,11]. A recent study has reported significantly fewer post-operative medical complications and reduced length of stay in the POPS patients, despite their great comorbidity.[33] This is supported by a systematic review of RCTs which shows the beneficial impact of CGA on post-operative outcomes.[34] The majority of our patients also demonstrated good functional outcome as evidenced by the high percentage of patients discharged home (79%). LS in our study was high (89% at 1 year) though our overall survival was low in keeping with the age and comorbidity of the cohort. This did not differ significantly from previously published studies, although it should be noted that our study analysed more distal (IP) revascularisation, which is previously reported to be associated with more comorbidities.

The current study shows that IP revascularisation is feasible, safe and effective as a treatment approach in the elderly CLI population. Independent living can be maintained in the majority of patients. However, despite the encouraging low perioperative mortality, high limb salvage rates and improved functional status, the results of revascularisation are limited by the poor life expectancy of this elderly high-risk group of CLI patients. This goes in line with a recent

multicentre analysis on nearly 1000 CLI patients undergoing endovascular therapy with follow up period longer than 24months, reported an estimated 2-year life expectancy less than 50% in high risk patients, with age being the strongest independent negative prognostic factor (OR: 3.7 for patients 80 years of age or older); the reported causes of death were cardiac (29%), vascular (10%), sudden death (8%), non-cardiovascular (46%) and unknown (7%).[35]

This analysis has the limitations of being a retrospective, single-centre study with potential selection bias. Further analysis allowing for comparative effectiveness of open bypass surgery versus best endovascular treatment in a cohort of elderly, high-risk patient is needed.

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CHAPTER 3.

Infra-Popliteal Bypass versus Angioplasty in patients with Critical Limb Ischaemia compared using Propensity Score Analysis

This chapter compares the outcomes of bypass surgery and endovascular treatment in the whole cohort of CLI patients with infra-popliteal disease by using a Propensity Score Analysis.

Awaiting for randomised controlled trials to publish their preliminary findings, statistical methods such as regression and propensity score models offer the best way to draw meaningful, evidence based conclusions to direct the treatment decision making.

Our data supports a pragmatic approach where patients with a suitable vein conduit and acceptable operative risk should be considered for bypass surgery; whereas in those with a higher operative risk an endovascular-first approach is recommended.

ABSTRACT

Background: Both infrapopliteal (IP) bypass surgery and endovascular intervention have been shown to have similar outcomes in patients with critical limb ischaemia (CLI), though there are no randomised trials to guide treatment choices. Our aim was to compare the outcomes of these treatments, after correcting for selection bias and confounding factors using Propensity Score (PS) analysis.

Materials and Methods: We compared outcomes in consecutive patients undergoing IP bypass (BS) and IP angioplasty (EV) for CLI (Rutherford 4-6) at a single institution following PS matching. The end points were primary, primary assisted and secondary vessel patency and amputation free survival (AFS) at 12 months using Kaplan Meier analysis.

Results: The initial cohort (n=279) differed significantly with respect to the incidence of diabetes (P=.024), eGFR (P=.006), total lesion length (P<.001) and Rutherford classification (P=.008). These factors were used to construct the PS model which yielded a matched cohort of 125 limbs in each group. Primary patency (P=0.014), assisted primary patency (P=0.003), secondary patency (P<0.001) and AFS (P=.043) were significantly better after BS compared to EV. However limb salvage was similar (P=.161), and overall complications (p=.04) as well as length of hospital stay (P=0.001) were worse in the BS group.

Conclusions: Our data supports a pragmatic approach where patients with a suitable vein conduit and acceptable operative risk are considered for bypass; whereas in those with a higher operative risk an EV strategy is considered first.

INTRODUCTION

The management of critical limb ischaemia (CLI) in patients with distal (infra-popliteal) arterial disease remains a major challenge. There is limited high-quality evidence to support treatment choices in this area with both bypass surgery and endovascular intervention shown to have good outcomes [1-3].

Infra-popliteal (IP) bypass surgery is associated with amputation free survival and patency rates approaching 80% at 1 year in experienced centres[4]. Overall survival and limb salvage rates vary between centres and range from 79-90% and 66-100% respectively at 1 year[4-6]. Data from randomised controlled trials is limited to the BASIL[7] and PREVENT III trials[8], the latter included 1404 patients with CLI with an infra-popliteal target vessel in 65% of cases. The primary patency, limb salvage and survival rates at 1 year were 61%, 88.5% and 83.8% respectively [8].

The BASIL and PREVENT III trials showed perioperative mortality rates to be 5.5% and 2.7% respectively [7-9], giving a clear insight into the risks associated with bypass surgery in an already elderly and co-morbid group of patients. This together with advances in balloon and stent technology have led many centres to support an endovascular first approach in patients with CLI due to IP disease [10;11]. Recent systematic reviews and meta-analysis of randomized trials have shown endovascular treatment to be technically feasible and relatively safe in this group of patients with a technical success rate up to 96%[2;3]. One year outcomes showed primary patency, secondary patency, limb salvage and overall survival were 66%, 74%, 88%; 88% respectively[2;3]. These results are comparable to IP bypass, though any such comparison is undermined by confounding factors and selection bias. Randomised controlled trials in this area will not report for several years and there is currently a lack of data offering

meaningful comparisons between the different treatment modalities. Our aim was therefore to compare outcomes in consecutive patients undergoing IP bypass surgery (BS) with those undergoing IP endovascular therapy (EV) for CLI patients in a single centre using propensity score analysis to allow valid comparisons to be made.

METHODS

We analysed the results for consecutive patients undergoing IP revascularisation for CLI (Rutherford 4-6)[12;13] in a single centre between 2010-2014. A prospectively collected database including patients' demographic, cardiovascular risk factors, angiographic findings, procedural variables and follow-up results (clinical and radiological) was analysed. Revascularisation strategy was stratified into BS or EV. Revascularisation was defined as IP if the distal anastomosis (in BS group) or target vessel recanalisation (in EV group) involved the anterior tibial (AT), tibio-peroneal trunk (TPT), peroneal artery (PeA), posterior tibial (PT), or dorsalis pedis (DP), with or without a concomitant inflow procedure. All patients gave informed consent, which included data collection. As per National Health Service Research and Ethics definitions (Institutional Review Board equivalent, http://www.nres.nhs.uk/) this study is not classified as research requiring formal ethics approval.

All patients with CLI were considered for revascularisation. Diagnostic imaging included duplex ultrasound as the first imaging modality, followed by CT-Angiography (CTA) or MR-Angiography as indicated. All patients were discussed in a dedicated multidisciplinary meeting (MDM) (including a diabetic foot MDM where appropriate) where the best revascularisation strategy was agreed upon, after careful consideration of patients' co-morbidities, availability of suitable venous conduit, anatomical distribution and extent of the disease. Within the EV group, 17 patients (13.6%) did not have an adequate vein conduit

Procedural Details

Technical details of the bypass procedure have been previously published [1;4]. Pre-operative duplex scanning was used to identify a venous conduit where possible, with the great saphenous vein (GSV) as the preferred conduit followed by the short saphenous vein (SSV) or arm veins (cephalic and basilic veins). Bypass grafts were tunnelled anatomically and used reversed or non-reversed (with valvulotome) as deemed appropriate depending on the size match between the vein and the inflow and outflow artery.

Endovascular interventions were performed either in a dedicated angiography suite or in hybrid theatre by consultant interventional radiologists or consultant vascular surgeons. The lesion was treated according to the operator's preference, preferentially intra-luminally by balloon angioplasty (Plain Balloon Angioplasty - PBA, Drug Coated Balloon - DCB) with stenting (Bare Metal Stenting - BMS, Drug Eluting Stenting - DES) being considered as a bailout option in case of suboptimal results.

For both BS and EV unfractionated heparin (100 IU/Kg) was given intravenously and additional boluses administered to maintain the activated clotting time (ACT) between 200 to 300 seconds. Patients received dual antiplatelet therapy immediately after the procedure for 3 to 6 months' unless contraindicated. Patients already on anticoagulation for a different medical condition were discharged on 75mg Aspirin in addition to their anticoagulant therapy. Patients were enrolled in our duplex surveillance programme consisting of scans pre-discharge and 3, 6, 9 and 12 months post-procedure and yearly thereafter, if no intervention was necessary for BS patients and scans at 6 weeks, 6 and12 months and yearly thereafter for the EV patients.

Study end points and statistical analysis

The primary end points were primary patency, assisted primary patency, secondary patency, amputation free survival (AFS) and limb salvage defined according to the published SVS reporting standards[13]. For the EV group, we defined *technical success per limb* defined as successful recanalisation of at least one tibial artery with straight in-line flow to the foot and residual stenosis <30% on completion angiography. T*echnical success per target vessel was* defined as immediate patency with residual stenosis <30% for each of the treated arteries.

Morbidity and mortality data was collected retrospectively and morbidity was further sub-classified using the Clavien-Dindo scale (Grade I- IV) [14]. Lesion length for the BS group was defined as the continuous length of artery bypassed. Lesion length for the EV group was defined as the length of treated artery. Where more than one infra-popliteal artery was treated then the shortest length achieving in line flow to the foot was taken. Measurements were done using CTA reconstructions on 3D workstations (Aquarius iNtuition Viewer, Aquarius, TeraRecon, San Matteo, CA, USA)

A propensity score model was constructed using logistic regression analysis. All pre-operative factors were compared in the two groups (BS and EV) and factors found to be statistically different ($P<0.05$) were then used to construct the model. The C statistic for the model (see results) was 0.78. Continuous variables are expressed as means ± standard deviation (SD) for parametric data and median (range) for non-parametric data and were compared using the independent samples T-test and the Mann-Whitney U test respectively. Categorical variables are presented as absolute values and percentages and were compared using the Chi-square test. Primary end points were analysed using Kaplan Meier Analysis, expressed as percentage survival (95% Confidence Interval) and compared using the log rank

test. A *P* value of <0.05 was considered statistically significant. All analyses were carried out using GraphPad Prism 6 (GraphPad Software Inc., San Diego, California) and SPSS 22 (IBM, New York, USA).

RESULTS

During the study period a total of 279 limbs in 243 patients underwent lower limb IP revascularisation for CLI (127 BS group, 152 EV group). Propensity score-matched cohorts were created and yielded a matched cohort of 125 BS and 125 EV patients. Characteristics of both original and propensity score-matched cohorts are listed in Table 1. The original cohort differed significantly from each other with respect to the incidence of diabetes (49% (n=62) vs 63% (n=96), P=.024), eGFR (74(±32) vs 63(±31) mls/min/m^3, P=.006) and total lesion (32(±13) vs 26(±12) cm, P<.001) in BS vs EV respectively. Rutherford classification was also significantly different in the groups (P=.008) with more tissue loss in the EV group (Table1). Although Femoro-politeal TASC classification was not significantly different in both groups (P=.138), the percentage of patients with no femoro-popliteal disease was significantly higher in the EV group (27% vs 45%, P=0.002).

Table 1. Pre-procedural characteristics of the cohort before and after propensity score (PS) matching

	Unmatched Cohort n=279			PS Matched Cohort n=250		
	BS (127)	EV (152)	P Value	BS (125)	EV (125)	P Value
Age (mean(SD) (yrs)	74(±10)	73(±13)	.562	74(±10)	73(±11)	.675
Sex (M:F)	92:35	101:51	.178	91:34	84:41	.439
IHD n(%)	31(24)	30(20)	.381	31(25)	25(20)	.451
Stroke/TIA n(%)	20(16)	20(13)	.648	20(16)	15(12)	.467
DM n(%)	62(49)	96(63)	**.024**	61(49)	69(55)	.378
Smoker n(%)	52(41)	60(39)	.967	52(42)	51(41)	.991
Hypertension n(%)	98(77)	108(71)	.272	96(77)	87(70)	.527
Hypercholesterolaemia n(%)	59(46)	60(39)	.273	58(46)	52(42)	.525
eGFR (mean(SD) (ml/min/1.73m^2)	74(±32)	63(±31)	**.006**	73(±32)	68(±31)	.144
Rutherford Category n(%)						
4	59(46)	49(32)		58(46)	43(34)	
5	56(44)	71(47)	**.008**	55(44)	61(48)	.092
6	12(9)	32(21)		12(10)	21(17)	
Femoro-Popliteal TASC n(%)						
A	2(2)	8(5)		2(2)	8(6)	
B	26(20)	17(11)	.138	24(19)	16(13)	.125
C	25(20)	25(16)		25(20)	21(17)	
D	40(31)	34(22)		40(32)	29(23)	
Tibial TASC n(%)						
B	0(0)	2(1)		0(0)	2(2)	
C	45(35)	38(25)	.242	43(34)	30(24)	.393
D	82(65)	112(73)		82(66)	93(74)	
Lesion Length(mean(SD) (cm)	32(±13)	26(±12)	**<.001**	32(±13)	28(±12)	.088

Binary logistic regression analysis was used to look for independent factors influencing the treatment decision between BS and EV (Table 2). A lower eGFR, shorter lesion length and the presence of diabetes were found to predict EV as the treatment. These factors in addition to Femoro-popliteal TASC classification and Rutherford stage were used to construct the Propensity score model. Table 1 shows that these factors are no longer found to be statistically different following PS matching, with the exception of the percentage of patients with no femoro-popliteal disease which remains significantly higher in the EV group (27% vs 40%, P=0.028).

Table 2. Binary logistic regression analysis showing pre-operative factors favouring Bypass Surgery as the treatment choice.

	Hazard Ratio	95% CI for HR	P Value
Diabetes	1.6	0.97-2.64	.043
eGFR	1.01	1.00-1.02	.010
Lesion Length	1.03	1.01-1.06	.001

(eGFR- estimated glomerular filtration rate)

Outcomes in the Matched Cohort

Indications for treatment in the matched cohort were Rutherford category 4 (46% vs 34%), 5 (44% vs 48%) and 6 (10% vs 17%) CLI (BS and EV groups respectively).

Target vessel for BS and EV groups is shown in Table 3. Proximal anastomosis was the common femoral (34%), above knee popliteal (44%), below knee popliteal (21%), or adjacent tibial (2%) arteries. Venous conduit was the GSV (90%), SSV (2%), Arm Vein (5%) or composite vein (3%). The vein was used reversed (48%) or non-reversed (52%) with a mean pre-operative diameter of 3.5(±1.5) mm.

Table 3. Target vessels in the Bypass Surgery (BS) and Endovascular Therapy (EV) Groups

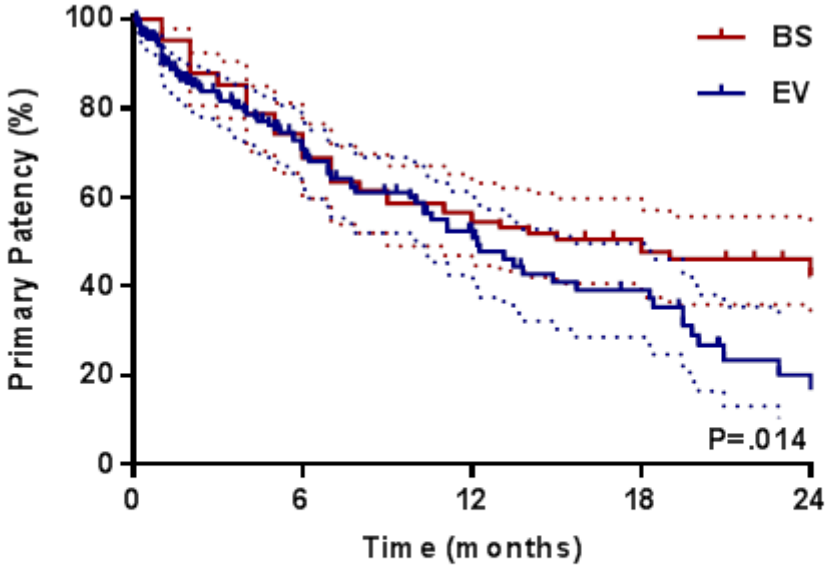
Target Vessel	BS n (%)	EV n (%)	P Value
TPT	25(20)	34(14)	.092
AT	33(26)	92(38)	
PT	34(27)	64(26)	
PeA	22(18)	54(22)	
DPA	11(9)	-	

(anterior tibial (AT), dorsalis pedis (DP), peroneal artery (PeA), posterior tibial (PT), tibio-peroneal trunk (TPT).

There were 244 IP endovascular target vessels. A single vessel was targeted in 42(33%) patients, with multiple vessels targeted in the remaining 83 (67%) patients. Treatment modality included PBA (92%), DCB (8%), BMS (2%) and DES (34%). At completion angiography, technical success per target vessel was 87%, and technical success per limb was 93%.

Comparing BS and EV, primary patency (54 (95% CI 44-63)% vs 51 (42-62)% at 1 yr, P=0.014), assisted primary patency (77 (70-86)% vs 63(54-74)% at 1 yr, P=0.003) and secondary patency (84(76-93)% vs 66(57-79)% at 1 yr, P<0.001) were significantly better after BS (Fig 1A-C).

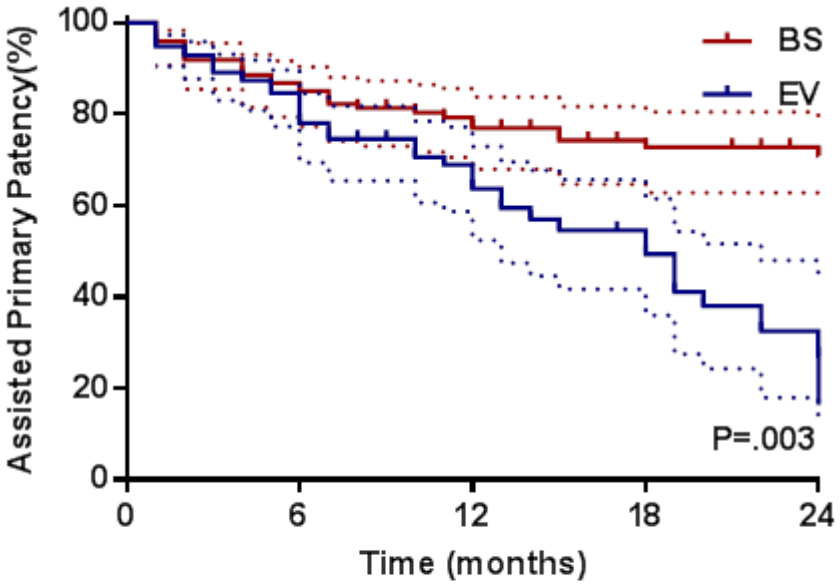
Fig1. Outcomes in Bypass Surgery (BS) and Endovascular Therapy (EV) compared using log rank test -
A Primary Patency, B Assisted Primary Patency and C Secondary Patency by Kaplan Meier analysis (interrupted lines represent 95% Confidence Intervals)



A

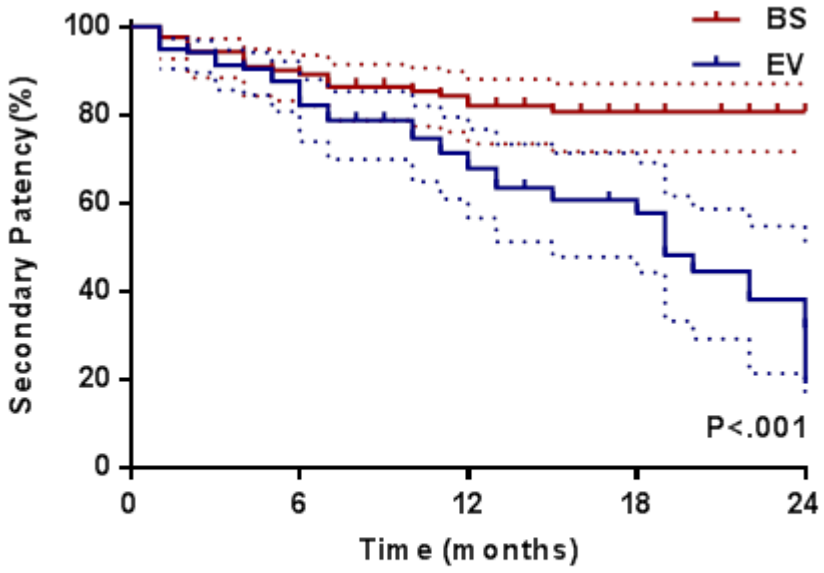
Numbers at Risk

BS	125	52	24
EV	244	37	6



B Numbers at Risk

BS	125	71	38
EV	244	39	6

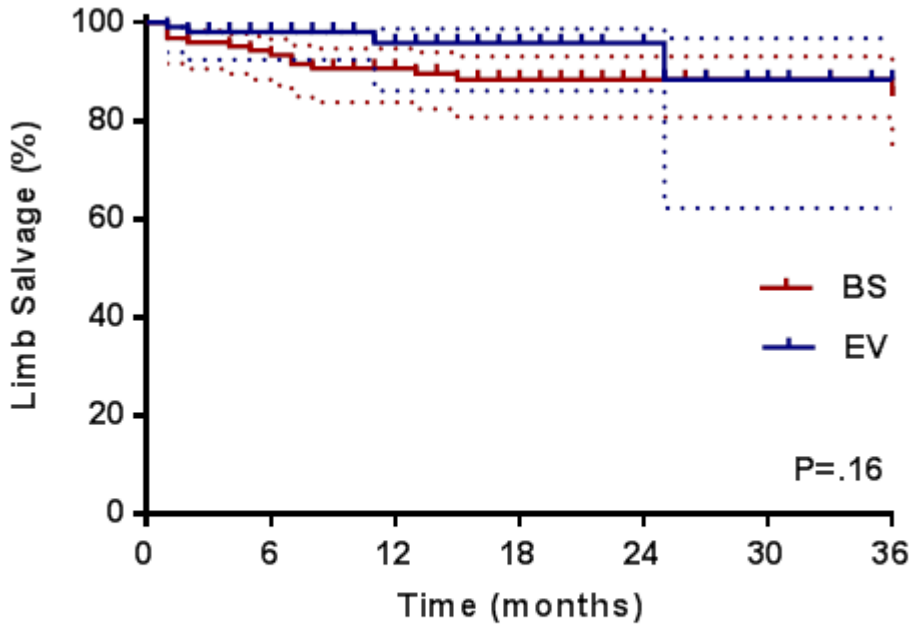


C Numbers at Risk

BS	125	75	41
EV	244	40	6

Freedom from re-intervention/target lesion revascularisation was similar in both groups (64(54-74)% vs 71(60-79)% at 1 yr, P=0.354). Over the study period there were 15 major limb amputations performed in the BS group and 6 in the EV, however follow up was significantly longer in the bypass group compared with the endovascular group (20 (±14) vs 10(±9), p=0.001). Kaplan Meier analysis showed that limb salvage was not significantly different between the groups (90(84-95)% BS vs 94(85-97)% EV at 1 yr, P=.161, Fig 2A). There were two mortalities in the first 30 days (2%) in the EV group and 1(1%) in the BS group. Overall survival (88(81-93)% vs 79(69-86)% at 1 yr P=0.004) and AFS (79(71-85)% vs 74(64-83)% at 1 yr, P=.043) by Kaplan Meier were significantly better in the BS group compared to the EV group (Fig 2B).

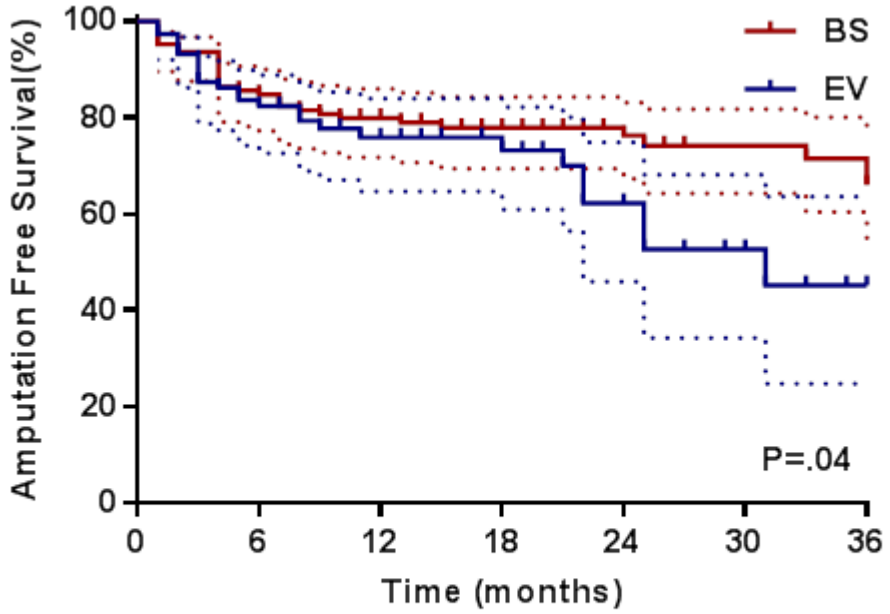
Fig 2. Limb Salvage (A) and Amputation Free Survival (B) compared in Bypass Surgery (BS) and Endovascular Therapy (EV) groups by Kaplan Meier analysis (log rank test, interrupted lines represent 95% Confidence Intervals)



A

Numbers at Risk

BS	125	90	49	26
EV	125	40	16	4



B Numbers at Risk

BS	125	90	49	26
EV	125	40	16	4

The most common peri-operative/procedural complications in BS group were wound infection (9%), Pneumonia (9%), arrhythmia requiring medical intervention (9%), acute kidney injury (6%), graft thrombosis requiring thrombectomy (4%) and urinary tract infection (4%). In the EV group these were acute kidney injury (4%), arterial rupture (3%), arterial dissection requiring an unplanned stent (3%), pseudoaneurysm (2%) and groin bleeding requiring surgical intervention (2%). Overall complication rates were higher in the BS group than the EV group (36% vs 22%, P=0.04).

When the morbidity was classified using the Clavien-Dindo grade and compared, minor complications (Grade I and II) were significantly more common in BS group (P=.028, RR 2.08, 95% CI 1.11-3.91) Table 4) whereas there was no difference in the incidence of major complications (Grade III-IV)(P=1.0, RR 1, 95%CI 0.44-2.29). The mean length of stay in hospital was also significantly longer in the BS group compared to the EV group (18(4-134) vs 5(0-110), P=0.001).

Table 4. Morbidity and mortality stratified using the Clavien-Dindo Classification

Complication Grade	BS	EV	P Value
I	12%	6%	**.028**
II	13%	4%	
III	9%	10%	.562
IV	1%	-	
V	1%	2%	.728

(Chi square based on minor- Grade I and II or major – Grade III and IV complications. BS – Bypass Surgery, EV - Endovascular)

DISCUSSION

We have attempted to compare the outcomes of BS and EV in the treatment of patients with CLI and IP disease by using Propensity score matching. We found that patency, amputation free survival and overall survival were significantly better in BS when compared to EV in the matched cohort. However limb salvage rates were similar and the incidence of complications and length of stay was higher in the BS group.

A recent update by the TASC steering committee[10], as well as the Task Force on the Diagnosis and Treatment of Peripheral Artery Disease of the European Society of Cardiology (ESC) recommended an endovascular first approach in patients with CLI and IP disease[15] . There are currently two randomised controlled trials (BEST-CLI [16] and BASIL-2[17] that will try and answer the question as to whether BS or EV have better results in the management of IP disease in patients with CLI. Until these trials publish their findings, statistical methods such as regression and propensity score models offer the best way to draw meaningful conclusions which help clinicians to make treatment decisions.

In this study the decision on the best revascularisation strategy was made in an MDT with surgeons and interventional radiologists and aided by information from specialist geriatricians who help assess and optimise our patients. In general, fitness for open surgical intervention, availability of a vein conduit, longer lesion length and good run-off are factors favouring open intervention. Conversely shorter lesion length, higher operative risk, and lack of a venous conduit favour endovascular intervention. This highlights the inherent confounders present when comparing treatment groups or studies outside of a randomised controlled trial. Propensity score matching has been used with success as a statistical method

to compare two treatment modalities in retrospective studies [18;19], and offers a method of minimizing selection bias and confounding factors. Other statistical methods are available that allow for this correction such as regression and case-control matching. However we chose PS analysis because unlike other methods which focus on outcome as the end point, PS analysis builds a model around the treatment option. There are many ways in which variables can be selected for inclusion in the PS model which intern can affect the validity of the model[20]., with some authors advocating including all variables related to the outcome as well as exposure[20;21]. We used a stepwise variable selection algorithm to develop a good predictive model. Our model included diabetes, eGFR, and total lesion length. These variables were major confounders at baseline level and were found on logistic regression analysis to be independent predictors determining whether a patient was more likely to have BS or EV treatment The Harrell's C statistic of 0.78 for this model was within the range of creating reliable propensity score-matched pairs (> 0.7) for BS and EV, indicating that a statistical analysis between the groups was valid. Finally the model also corrected for the baseline confounding factors following PS matching. Our results showed that successful restoration of straight-line-flow down to the foot (technical success per limb) was achieved in 93% of the cases in the EV group. A contemporary meta-analysis reported a technical success of 92.3% following primary IP angioplasty.[3] Furthermore a meta-analysis of randomized controlled trials [2] reported primary patency, secondary patency and AFS rates at 1 year to be similar to those in the present study (51% - present study vs. 57.1%-65.7%; 66% vs. 57.6%-73.5%; *78% vs. 66.2%-75.0%*, respectively). Similarly following IP bypass the primary and secondary patency rates, and amputation free survival at 1 year were similar in the present study compared to other large contemporary series (54% present study vs 61-62%%, 84% vs 87-88% and 80% vs 83%)[4;22].

Our results show that the higher patency rate in the BS group did not lead to a higher limb salvage rate or a higher freedom from re-intervention rate. A recent systematic review of IP revascularisation also found better patency though similar limb salvage rates when comparing infrapopliteal bypass surgery with angioplasty [23]. This is perhaps a reflection of the fact that achieving limb salvage is dependent on a number of different factors other than a technically successful revascularisation, such as the degree and pattern of tissue loss, patient co-morbidities, and variation in the pathogenicity and treatment of the any superimposed wound infection.

Life expectancy remains poor in CLI patients as shown by the mortality rate in this study of 16% at 1 year, which is in keeping with the results of a metanalysis of prospective studies which showed overall mortality rates of 17.5% at 1 year and 35% at 3 years regardless of the treatment strategy[24]. In addition the mortality rate in our study was significantly higher in the EV group compared to the BS group. The mode of revascularisation was selected based on MDM discussions rather than a randomized process and there is a natural tendency to select fitter patients to undergo BS and this may be reflected in the better long term survival in this group. Given that limb salvage was the same in both groups, this may also explain why AFS was better in the BS group.

Using the Clavien Dindo scale we found that the incidence of minor complications (Grade I and II) was significantly higher in the BS group, whereas the incidence of major complications (Grade III and IV ~10%) and peri-operative mortality were not significantly different between the two groups. A direct comparison of complications following lower limb bypass or endovascular intervention (US Medicare population)[25] found that although mortality rates were higher following bypass (0.79% vs 0.48%), overall risk of adverse

complications was significantly higher in the endovascular group (8.5% vs 7.7%). These numbers are broadly in agreement with the incidence of complications encountered in the present study in both BS and EV groups. This highlights that both treatment modalities have associated risks, which should be considered carefully in the decision making process.

The main limitation of our study is that it is not a randomised controlled trial. Propensity score matching attempts to reduce the effect of bias and confounding factors by producing two equal cohorts based on the pre-operative variables. Despite matching for co-morbidities we found that long term survival was significantly lower in the EV group. This may reflect a tendency to offer EV approach to high-risk patients who naturally have a shorter life-expectancy. The obvious mismatch that was still present even after Propensity score matching was the higher percentage of patients with femoro-popliteal disease in the BS cohort. However this would bias in favour of poorer results in the BS group, whereas BS has been shown to have better long term outcomes compared to EV. Finally we acknowledge that the slight differences in the duplex surveillance intervals may have led to differences in the detection and treatment of restenotic lesions between the two treatment groups. However it should be noted that overall there was no difference in the freedom from re-intervention/TVR between BS and EV

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CHAPTER 4.

Salvage Interventions on Threatened Infra-Popliteal Bypass grafts: impact on Patency and Amputation Free Survival

Distal bypass surgery is effective at achieving limb salvage though secondary interventions maybe required to maintain graft patency. We present medium term data on these secondary interventions and show that half of all grafts require endovascular salvage interventions. However these interventions have a high success rate and we show that this translates not only to improved patency but also maintains amputation free survival and limb salvage rates that compare to non threatened

ABSTRACT

Objectives: Infra-popliteal bypass is an established and effective method for limb salvage in patients with critical limb ischaemia (CLI). Secondary interventions maybe required in order to maintain graft patency. The aim of this study was to look at the frequency and outcomes of such interventions.

Materials and Methods: Consecutive patients undergoing bypasses onto the infra-popliteal vessels for CLI (Rutherford 4-6) at a single institution were analysed between 2009-2013. The primary end points were graft patency, limb salvage and amputation free survival at 12 months by Kaplan Meier analysis.

Results: A total of 122 infra-popliteal bypasses were performed in 108 patients. Distal anastomosis was on to the anterior tibial (n=37), posterior tibial (n=28), peroneal (n=24), tibio-peroneal trunk (n=24) or dorsalis pedis artery (n=9). Primary patency, assisted primary patency and secondary patency was 56%, 73% and 81% respectively at 12 months and 44%, 68% and 78% respectively at 24months. Amputation free survival was 79% at 12 months and 73% at 24 months. Endovascular salvage interventions performed on 61(50%) graft included angioplasty of inflow/proximal anastomosis (28%), outflow/distal anastomosis (39%), graft stenosis (17%) and thrombolysis (17%). Amputation-free survival was similar in salvaged threatened and acutely occluded grafts compared to non-threatened grafts (Log rank test, P=0.064) and better in grafts requiring re-intervention later (>6months from bypass) compared to those requiring early re-intervention (<6months, P=0.047).

Conclusions: Secondary interventions in threatened distal bypass grafts are successful at maintaining graft patency and amputation free survival with a low morbidity rate.

INTRODUCTION

The prevalence of critical limb ischaemia (CLI) is estimated at 1% of the population aged 60 years or older, with the percentage increasing with age[1]. The 1 yr outcomes for patients who develop CLI are very poor with a mortality rate of 25% and an amputation rate of 30%[1]. Despite advances in endovascular management, infrapopliteal bypass surgery remains an established and effective method of achieving limb salvage especially for long segment occlusions or after failed endovascular interventions.

Distal bypass surgery is associated with amputation free survival and patency rates approaching 80% at 1 year in experienced centres[2]. There is increasing evidence that these grafts require long term surveillance to detect those at risk of thrombosis, though the advantage of duplex surveillance over clinical monitoring is still controversial[3]. However it is clear that improvements in duplex ultrasound scanning technology and increased surveillance of grafts can accurately detect significant stenosis that threaten their patency[4, 5]. Subsequent secondary interventions occur in around 30% -50%[2, 6] of grafts and include angioplasty of inflow, outflow or graft stenosis, thrombolysis or surgical interventions with an overall technical success over 90%[7, 8]. For distal bypasses this improves the patency of grafts at 1 yr from 62 % (primary) to 83% (assisted primary). However there is still a paucity of data regarding the frequency, timing and optimal management particularly in threatened distal bypass grafts. The existing studies also suffer from lack of long term follow up and have yet to prove that intervention has a clinically detectable benefit. In this study we aim to report medium term results of salvage interventions on threatened distal bypass grafts and assess the impact on long term patency and amputation free survival.

METHODS

A prospectively collected bypass database was screened to identify consecutive patients that underwent a distal bypass for critical limb ischaemia (Rutherford 4-6) in a single centre between 2009-2013. Distal bypass was defined as any bypass with a distal anastomosis onto the tibio-peroneal trunk (TPT), posterior tibial (PT), anterior tibial (AT), dorsalis pedis (DP) or peroneal (PeA) arteries. Patient demographics, operative details, and follow-up information was collected retrospectively along with details of subsequent secondary interventions. These were identified by searching the hospital electronic patient record which includes all hospital visits, results of all investigations and treatments. All patients gave informed consent, which included data collection. Formal ethics approval was not required given the retrospective nature of the study and that no research was conducted on patients.

Operative details

Technical details of the bypass procedure have been previously published[2]. Briefly, all patients with CLI underwent pre-operative imaging which was reviewed in a multi-disciplinary team meeting before bypass surgery. Pre-operative duplex scanning was used to identify a venous conduit where possible with the great saphenous vein (GSV) as the preferred conduit over short saphenous vein (SSV) or arm veins (cephalic and basilic). Bypass grafts were tunnelled anatomically, and reversed or non reversed (with valvulotome) as deemed appropriate depending on the size match between the vein and the inflow and outflow artery. Unfractionated heparin was given intravenously (1 mg/kg) before vessel clamping and additional boluses administered to maintain the activated clotting time (ACT) between 200 to 300 seconds. All patients received treatment dose low molecular weight

heparin until a satisfactory post-operative duplex scan, upon which patients were discharged on dual antiplatelet agents for 3 months.

Identification and treatment of threatened grafts

All patients were enrolled in our duplex surveillance programme consisting of scans pre-discharge and 3, 6, 9 and 12 months post-operatively if no intervention was necessary. Duplex criteria for intervention were a stenosis >70%, with peak systolic velocity(PSV)<45cm/s or >300cm/s, or when the velocity ratio > 4.0[9].

Graft definitions:-

Threatened graft (TG) – any graft with duplex evidence of a significant stenosis that threatens patency.

Acutely occluded graft (AOG) – any graft which occludes acutely presenting as symptomatic lower limb ischaemia.

Non threatened (NTG) graft - a patent or occluded graft without prior duplex evidence of a significant stenosis. This group included patients with occluded grafts found on surveillance duplex which remained asymptomatic.

Patients with threatened grafts were offered immediate DSA and treatment if a significant stenosis was confirmed. Ipsilateral or contralateral access was chosen so as to optimise access depending on the site of the lesion as seen on duplex. The lesion was crossed with a 0.035-inch or 0.018-inch guidewire over which a standard PTA balloon was advanced, the diameter of which was chosen to match the adjacent vessel (2-7mm). In cases of residual stenosis or

flow limiting dissection after PTA, stent placement was performed. Drug coated balloons (DCB) and drug eluting stents (DES) were placed for recurrent stenosis. Symptomatic patients presenting with graft occlusion, confirmed on duplex or CTA, went onto to have catheter directed thrombolysis with tissue plasminogen activator (tPA). These patients had repeat DSA to monitor progress of thrombolysis and to identify significant stenosis which was then treated as above. Following secondary intervention patients were discharged home on their preoperative antiplatelet regimen and continue the duplex surveillance protocol as new until they complete a year without re-intervention, and then yearly scans thereafter.

Study end points and statistical analysis

The primary end points were graft primary patency, assisted primary patency, secondary patency, amputation free survival (AFS) and limb salvage using Kaplan Meier analysis and defined according to the published SVS reporting standards[10]. Technical success was defined as a less than 30% residual stenosis on completion angiogram. Continuous variables are expressed as means ± standard deviation (SD) for parametrically distributed data and median (range) for non parametric data, whereas categorical variables are presented as absolute values and percentages. The primary end points were compared using the log rank test.

A P-value of <0.05 was considered statistically significant. All analyses were carried out using GraphPad Prism 6 (GraphPad Software Inc., San Diego, California) and SPSS 22 (IBM, New York, USA).

RESULTS

A total of 122 distal bypasses were performed in 108 patients with 4 additional patients lost to follow-up, who were excluded from analysis. Patient demographics and cardiovascular risk factors are listed in Table1.

Table 1. Pre-procedural demographics and cardiovascular risk factor (IHD-Ischaemic heart disease, DM – diabetes mellitus, CRF – chronic renal failure, TIA – transient ischaemic attack)

Age (mean±SD)	73 (±11)
Sex (M:F)	77:31
IHD (%)	33 (31)
Previous Stoke/TIA (%)	16 (15)
DM (%)	53 (49)
Smoker (%)	40 (37)
Hypertension (%)	83 (77)
Hypercholesterolaemia (%)	45 (42)
CRF (%)	35 (32)
eGFR (ml/min/1.73m^2)	75 (±35)

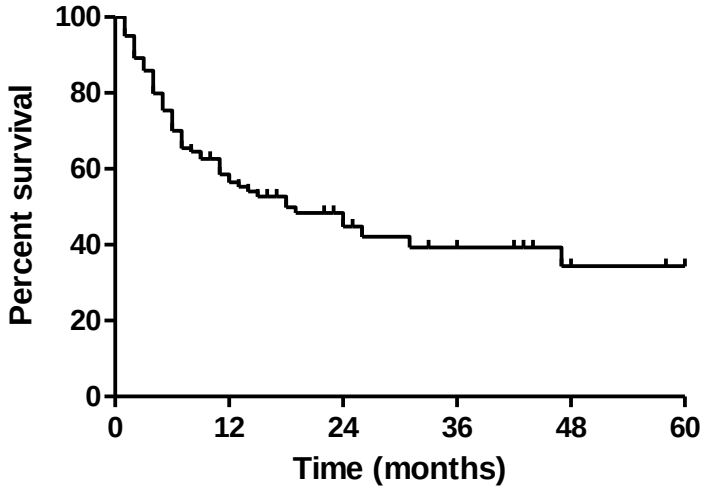
Indications for treatment were Rutherford stage 4 (49%), stage 5 (39%) or stage 6 (12%) critical limb ischaemia. The characteristics of the bypasses are listed in Table 2.

Table 2. Bypass Characteristics
(Superficial femoral artery-SFA, Popliteal artery-POP, Tibio-peroneal trunk-TPT)

Conduit	
Great saphenous vein	105 (86)
Arm vein	6 (5)
Short saphenous vein	3 (2)
PTFE (+ vein patch)	8 (7)
Vein graft reversed	56 (49%)
Size of vein graft (mm)	4 (±0.98)
Proximal anastomosis	
Common Femoral Artery	45 (37)
SFA/ Above knee POP	51 (41)
Below knee POP/TPT	17 (14)
Previous Femoro-popliteal bypass	9 (7)
Distal anastomosis	
Tibio-peroneal trunk	24 (20)
Anterior tibial	37 (30)
Posterior tibial	28 (23)
Peroneal	24 (20)
Dorsalis Pedis	9 (7)

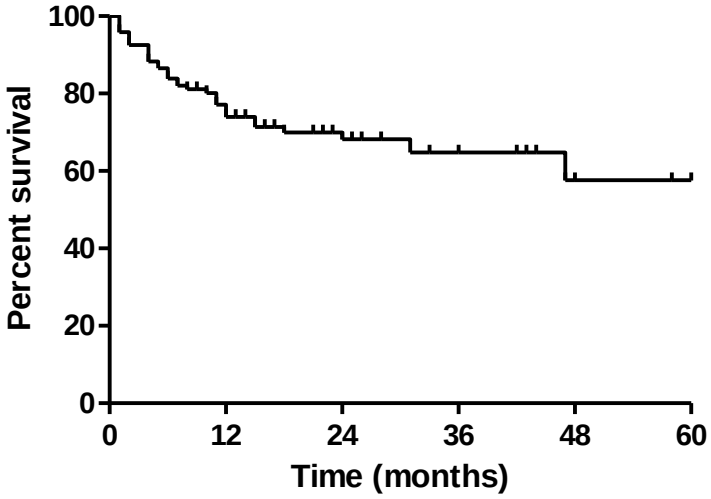
The mean follow up was 21(±14) months and primary patency, assisted primary patency and secondary patency was 56%, 73% and 81% respectively at 12 months and 44%, 68% and 78% respectively at 24months (Figure 1 A,B and C).

Figure 1. A. Primary patency, B. Assisted primary patency, C. Secondary patency by Kaplan-Meier analysis.



Numbers at risk

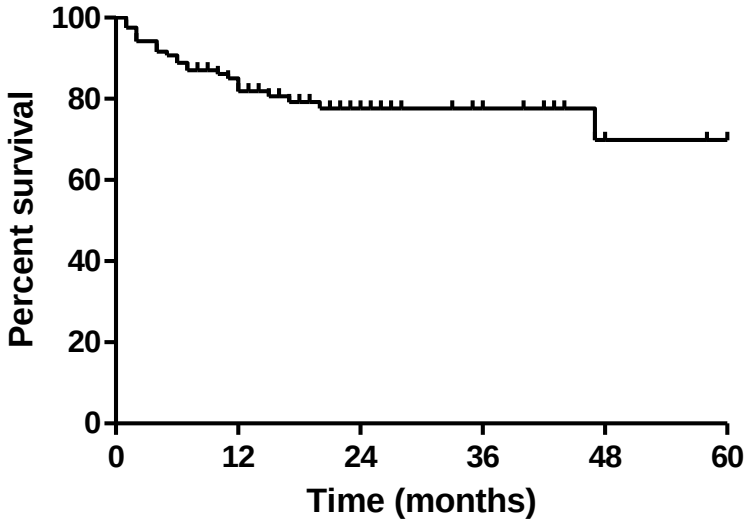
122	55	27	13	6	2



B

Numbers at risk

122	73	40	18	7	2



C

Numbers at risk

122	80	44	20	8	2

Amputation free survival was 79% at 12 months and 73% at 24 months. There were 16 major limb amputations performed at a median of 7(1-47) months from bypass surgery. The 12 month limb salvage rate was 91%, and overall limb salvage rate was 87% over the follow up period. There were 23 deaths over the follow up period, with 30 day and 1year mortality rate of 0.8% (1 patient) and 13% respectively by Kaplan Meier analysis.

There were 61(50%) grafts classified as non threatened, 44(36%) threatened grafts and 17(14%) acutely occluded grafts. (Table 3). Median time from bypass to first intervention was 5(1-46) months.

Threatened grafts underwent 76 percutaneous endovascular procedures with an overall technical success rate of 90.7%. There were 7 technical failures (9.2%) resulting in surgical revision of the anastomosis in 3 (2.5%) grafts, and a jump graft to a more distal tibial vessel in 4(3.2%) grafts. A further 4(3.2%) patients underwent jump grafts as they were not deemed suitable for endovascular treatment.

Table 3. Secondary interventions on threatened and acutely occluded grafts

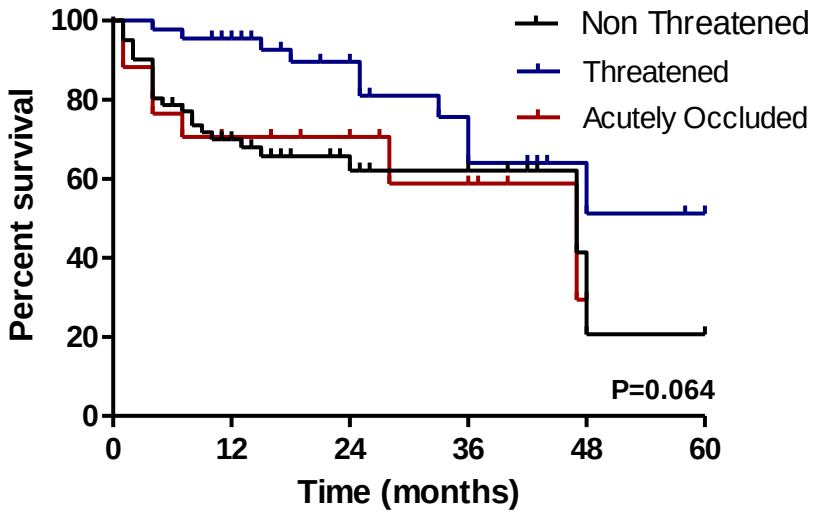
Endovascular	
Lesion Location	
Inflow	16 (19)
Outflow	18 (21)
Proximal anastomosis	12 (14)
Distal anastomosis	21 (25)
Graft	17 (20)
Treatment modality	
Baloon angioplasty only	65 (77)
Drug containing baloon	12 (14)
Bare stent	5 (6)
Drug eluting stent	2 (2)
Thrombolysis	14
Surgical	
Thrombectomy	3
Jump graft	8
Surgical revision of proximal anastomosis	2
Surgical revision of distal anastomosis	1

Over the follow up period 17 patients presented acutely with occluded grafts, which resulted in 14 grafts being treated with thrombolysis (and subsequent angioplasty) and three with thrombectomy. Thrombolysis was successful in 13 patients, giving a technical success rate of 93%. There were no mortalities within 30 days of the secondary procedure. Morbidities included pseudoaneurysm at the puncture site (5%, managed with thrombin injection) and distal anastomosis site (1%) which required a covered stent. Thrombolysis was stopped early due bleeding in a further 2% of cases.

Out of 61 non threatened (non intervened) grafts, 51 were fully patent at the end of the study period, with 10 (16%) occluding in the surveillance intervals. Out of the 44 threatened grafts, 22 (50%) had a single intervention, 22 (50%) went on to have multiple procedures, and 7 (16%) grafts occluded by the end of the study period. Of the 17 acutely occluded grafts 8 (47%) went on the have multiple endovascular procedures with 7 (41%) grafts occluding by the end of the study.

Amputation-free survival was higher in threatened grafts when compared to non threatened and acutely occluded grafts (N= 61 vs 44 vs 17 , Log rank test, P=0.064, Figure 2) though this did not reach statistical significance (NTG vs TG HR 0.42 (95% CI 0.20-0.84), NTG vs AOG HR 0.94 (95%CI 0.39-2.25), TG vs AOG HR 2.35 (95% CI 0.78-7.09), Limb salvage was similar in all groups (P=0.13).

Figure 2. Amputation free survival in non threatened, threatened and acutely occluded grafts (log rank test)

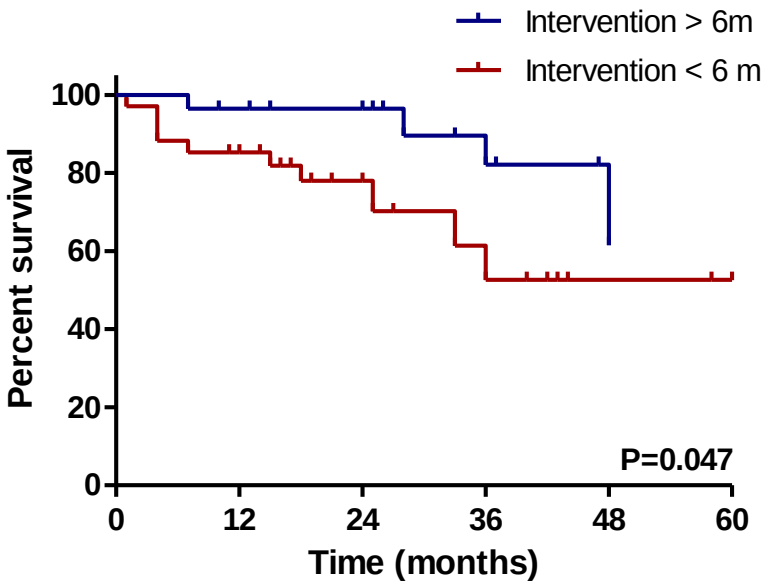


Numbers at risk (SE of survival)

NT	61	37(6)	18(6)	10(7)	2(17)	1(17)
T	44	38(3)	27(5)	13(10)	5(14)	1(14)
AO	17	12(10)	9(10)	5(14)	1(21)	-

Amputation free survival was significantly worse in grafts having early intervention (< 6months) compared to later intervention (> 6months, N=33 vs 28, P=0.047, HR 2.97 (95% CI 1.00-8.71, Figure 3). We performed a Cox regression analysis to look for factors significantly affecting the primary end points and a binary logistic regression analysis to find variables predicting need for re-intervention. Factors included were all patient demographics, bypass characteristics and secondary intervention variables as per Tables 1-3, but no factors were found to independently predict outcome

Figure 3. Amputation free survival in patients with early intervention (<6months) compared with later intervention (>6months)



Numbers at risk (SE of survival)

> 6 months	28	26(4)	21(4)	12(9)	4(19)	-
< 6 months	33	27(6)	16(7)	7(13)	3(13)	1

DISCUSSION

The treatment of threatened bypass grafts has changed significantly over the past decade, with a variety of endovascular techniques now available to treat stenosis and open occluded grafts, thereby maintaining graft patency and preventing limb loss. Here we have presented a series of salvage interventions on distal bypass grafts using balloon angioplasty, drug coated balloons, nitinol stents, drug eluting stents and thrombolysis with an overall technical success over 90%. Most importantly we have shown that once a threatened graft is detected, intervention can lead to amputation free survival and limb savage rates that are comparable to patients with grafts that do not undergo any intervention. Our study has also demonstrated that grafts requiring early interventions (< 6months) have poorer outcomes. Whereas previous studies have only been able to demonstrate that the need for earlier intervention leads to reduced overall patency[8], we are the first to show that this also leads to a worse amputation free survival.

Several authors have reported on endovascular and open surgical salvage of threatened bypass grafts, but none have focused on distal bypasses. In a study comparing outcome of surgical and endoluminal intervention for anastomotic strictures in infra-inguinal bypasses, the authors concluded that open surgical repair led to fewer subsequent re-interventions compared to angioplasty[11]. Secondary patency rates at 3 years was 51% in the angioplasty group and 56% in the operative group. There was a clear bias in favour of the surgery group as two thirds of the grafts presenting with thrombosis were treated endovascularly. The relatively high incidence of re-interventions is clearly a disadvantage of endovascular therapy and this has led some authors to state that surgical repair, particularly of anastomotic lesions, should be the treatment of choice.[12] A recent series looking at endovascular treatment of

anastomotic stenosis reported assisted primary patency rates of 85% at 2 years[8] but this study excluded patients treated for occluded grafts and included only 15 patient with infra-popliteal distal anastomosis. Studies looking at angioplasty of distal anastomosis alone have reported an assisted primary patency rate of 53% after 3 years[13]. Angioplasty of in-graft stenosis has been reported to have an assisted primary patency rate of 65% at 5 years[14]. These studies are difficult to compare directly with ours given that our study includes only distal bypass grafts undergoing multi-modality therapy for multilevel stenosis. However the studies are in broad agreement in showing that endovascular therapy has a high technical success rate with acceptable long term patency. Patients undergoing distal bypass tend to have a higher number of co-morbidities, particularly diabetes and renal failure[2], and these patients have the most to gain from minimally invasive graft salvage techniques. The percentage of grafts requiring single (26%) or multiple (24.5%) re-interventions was higher than expected in our study, though it should be noted that the morbidity from these interventions was low and technical success rate was high. Similarly another study found that only 37% of the patients were free from graft restenosis at 12 months and 31% at 24 months after the first intervention though again with good technical success and low overall morbidity[15]. As such we feel that endovascular therapy should be considered the first line treatment of threatened grafts if suitable. Surgical graft salvage is still an option in selected patients after failed endovascular interventions, though in our series this was necessary in only 11% of grafts.

Drug coated technology shows great promise in preventing restenosis and both the THUNDER[16] and the FemPac[17] studies demonstrated significant reduction of binary restenosis and TLR rates, which where sustained at up to 2-year follow-up. However there is little evidence to support their use in anastomotic or graft stenosis, and a study from our institution comparing drug coated balloons with normal balloons used to treat anastomotic

stenosis in threatened femoro-popliteal bypass grafts found no difference in restenosis rate or freedom from target lesion revascularisation[18]. As such we reserve the use of this technology in only recurrent lesions not responding to balloon angioplasty.

All re-interventions are dependent upon the surveillance protocols that are in place to detect threatened grafts, and we adhere to a strict duplex surveillance protocol in our unit. A systematic review of 6649 vein grafts comparing duplex with clinical surveillance[5] found that the total number of deaths, occluded grafts and the number of occlusions after 30 days were significantly greater in those not undergoing surveillance. However, surveillance did not improve the limb salvage rate. Surveillance may not be expected to improve limb salvage or AFS in threatened grafts compared to non threatened grafts but rather maintain it by allowing early recognition and treatment of critical stenosis. A randomised controlled trial (RCT) of 156 patients following femoropopliteal/ crural vein bypass surgery showed that duplex scans every 3 months for 2 years, with an additional scan at 3 years significantly improved assisted primary cumulative and secondary patency rates at 3 years.[19] However a further RCT of 594 patients who underwent femoropopliteal/ crural vein bypass showed no difference in primary patency, secondary patency and most importantly, amputation rates between duplex surveillance and clinical monitoring.[4]Comparing non threatened, threatened and acutely occluded grafts undergoing intervention in our series shows that the amputation free survival is not significantly different in these groups, but with a trend towards better outcome in threatened grafts. This may be because primary occlusion represents a failure of graft surveillance and therefore patients in whom threatened grafts are detected and subsequent intervention carried out present with a trend towards a better outcome.

We acknowledge the limitations of our study in particular the retrospective nature. The number of bypasses in our study undergoing a single intervention for a single level of disease was too few to undertake a subgroup analysis. A large prospective randomised study would clearly be ideal to elucidate the optimal treatment strategy for different levels of stenosis. However such a study would require a prohibitively large number of bypass grafts, over a long period of time which in itself poses problems given the rate at which endovascular techniques are evolving.

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CONCLUSIONS

This thesis has investigated the role of Complex Infra-Popliteal (IP) Revascularisation in a large cohort of over 250 consecutive patients presenting with critical limb ischaemia (CLI) who have been treated at St Thomas' Vascular Unit.

A technical and clinical outcome of 127 distal bypasses and 201 tibial angioplasties on 393 target vessels have been analysed.

In **Chapter 1** our results showed that post-procedural dual antiplatelet therapy (DAPT) is a predictor of better AFS and F-MALE following IP endovascular treatment in CLI patients. Old age and poor eGFR are predictors of worse AFS. These findings highlight the importance of pre-procedural medical optimisation and appropriate pharmacological management which can potentially improve clinical outcome. IP endovascular treatment has satisfactory mid-term technical and clinical outcomes; however 2-year overall survival is relatively low in this high risk group.

Chapter 2 evaluated the feasibility, safety and effectiveness of IP revascularisation as a treatment approach in the elderly (over 80 years of age) CLI population. Independent living can be maintained in the majority of patients. By adopting a patient-tailored approach, both bypass surgery and endovascular treatment have satisfactory technical and clinical outcomes in this high-risk group. Subgroup analysis suggests that bypass surgery may have better mid-term secondary patency and AFS rates. However, despite the encouraging low perioperative mortality, high limb salvage rates and improved functional status, the results of revascularisation are limited by the poor life expectancy of this elderly high-risk group of CLI patients.

In **Chapter 3** a Propensity Score Analysis provided a strong level of evidence when comparing the outcome of bypass surgery (BS) and Endovascular treatment (EV), after correcting for selection bias and confounding factors. Both IP BS and EV have been shown to be effective with good medium-term outcomes in patients with CLI. IP bypass surgery has been shown to have better patency rates, AFS and overall survival, but also higher complication rates and hospital stay. Most importantly there was no difference in the limb salvage rates between the two groups. Our data supports a pragmatic approach where patients with a suitable vein conduit and acceptable operative risk should be considered for BS; whereas in those with a higher operative risk an EV first approach is recommended.

Chapter 4 highlighted the importance of secondary interventions (angioplasty) in threatened distal bypass grafts at maintaining graft patency and clinical outcome with a low morbidity rate. Timely intervention based on an endovascular-first strategy maintains graft patency and amputation free survival in threatened grafts which is comparable to non-threatened grafts.