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Procedural and 12 month in-hospital costs of primary infra-popliteal bypass surgery, infra-popliteal best endovascular treatment, and major lower limb amputation for Chronic Limb Threatening Ischaemia

Short-title: Micro-costing in Chronic Limb Threatening ischaemia secondary to infra-popliteal disease.

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ARTICLE HIGHLIGHTS

Type of Research: Single centre prospective observational study.

Key Findings: In 60 patients undergoing treatment for CLTI, bypass surgery (BS) and major lower limb amputation (MLLA) were significantly more expensive than best endovascular treatment (BET) in terms of human resources (BS £2,551 vs. MLLA £1,130 vs. BET £329) and in-hospital costs (MLLA £13,320 vs. BS £8,714, vs. BET £4,813).

Take home Message: In terms of calculated procedural HR and in-hospital costs, both IP VB and MLLA are more expensive than IP PBA. These data together with QALY data from BASIL-2 will help inform the calculation of incremental cost-effectiveness ratios for different CLTI management strategies.

Table of contents summary: In this prospective study of 60 patients with infra-popliteal disease, over a 12 month time horizon, best endovascular treatment is cheaper in terms of human resources and in-hospital costs than major lower limb amputation or bypass surgery.

ABSTRACT

Background
Chronic limb threatening ischaemia (CLTI) is a growing global problem due to the widespread use of tobacco and increasing prevalence of diabetes. Although the financial consequences are considerable, few studies have compared the relative cost-effectiveness of different CLTI management strategies. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL)-2 trial is randomising CLTI patients to primary infra-popliteal (IP) vein bypass surgery (BS) or best endovascular treatment (BET) and includes a comprehensive within-trial cost-utility analysis.

**Aim**

To compare over a 12-month time horizon, the costs of primary IP BS, IP best endovascular treatment (BET), and major limb major amputation (MLLA) to inform the BASIL-2 cost-utility analysis.

**Methods**

We compared procedural human resource (HR) costs and total in-hospital costs for the index admission, and over the following 12-months, in 60 consecutive patients undergoing primary IP BS (n=20), IP BET (n=20), or MLLA (10 transfemoral and 10 transtibial) for CLTI within the BASIL prospective cohort study.

**Results**

Procedural HR costs were greatest for BS (BS £2,551, 95% CI: £1,934–2,807 vs. MLLA £1,130 95% CI: £1,046–1,297 vs. BET £329, 95% CI: £242-390, p<.001, Kruskal-Wallis) due to longer procedure duration and greater staff requirement. With regard to the index admission, MLLA was the most expensive due to longer hospital stay (MLLA £13,320, 95% CI: £8,986-18,616 vs. BS £8,714, 95% CI: £6,097-11,973 vs. BET £4,813, 95% CI: £3,529-6,097, p<.001, Kruskal-Wallis). The total cost of the index admission and in-hospital care over the following 12-months remained least for BET (MLLA £26,327, 95% CI: £17,653-
30,458 vs. BS £20,401, 95% CI: £12,071-23,926 vs. BET £12,298, 95% CI: £6,961-15,439, p<.001, Kruskal-Wallis).

Conclusion

Over a 12-month time horizon, MLLA and IP BS are more expensive than IP BET in terms of procedural HR costs and total in-hospital costs. These economic data together with quality of life data from BASIL-2 will inform the calculation of incremental cost-effectiveness ratios for different CLTI management strategies within the BASIL-2 cost-utility analysis.

Keywords:

Chronic Limb Threatening Ischaemia, Costing, Endovascular, Surgery, Amputation

The authors have no conflict of interests to declare

The BASIL-2 trial is funded by the UK NIHR HTA
INTRODUCTION

Chronic limb threatening ischaemia (CLTI)\(^1\) is an increasing global health and social care problem due to widespread tobacco use and the growing prevalence of diabetes. Patients usually present with complex, multi-level disease, that increasingly involves the infra-popliteal (IP) arteries. The financial consequences of this growing CLTI burden are considerable, especially for low- and middle-income countries (LMIC)\(^1,2\). In the UK, the total annual direct healthcare cost of caring for CLTI patients has been estimated at £200 million, but this is likely to be a significant underestimate of the true overall financial burden of the disease\(^3\). In the US, this figure is estimated to be in the range of US$10-20 billion\(^4\). The annual cost of revascularisation for CLTI in the US has been estimated at US$4.2 billion per year, with an additional US$625 million spent on unplanned re-admissions in the 30-days following intervention\(^5\). The cost of a CLTI admission in the US has been estimated at around US$23,000\(^6\). Evidence suggests that all these costs are increasing rapidly\(^7\). Despite this, there are surprisingly few published studies that have examined the relative costs and cost-effectiveness of the three main primary interventions for CLTI: bypass surgery (BS), best endovascular treatment (BET) and major lower limb amputation (MLLA). This is perhaps because of the difficulty of accurately estimating the true cost of each component of care in the context of a complex patient journey that often involves repeated re-admissions and further procedures, as well as community care, over several years\(^8,9\).

In the UK Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL)-1 trial, the mean overall hospital costs in the 12 months following randomisation were significantly higher after BS (US$34,378) than plain balloon angioplasty (PBA) (US$25,909)\(^9\). However, due to more hospital admissions and further procedures after PBA, the cost difference reduced to US$5,000 at three years (bypass $45,322 vs. PBA $39,801) and was not significant. Even fewer economic data are available for CLTI patients undergoing MLLA. One study estimated the in-patient cost at around US$40K based on median stay of 9 days\(^10\).
The only published study of long-term costs following primary MLLA for CLTI suggests it is around $80K over 10 years\textsuperscript{11}. However, estimating long-term costs is challenging given the poor overall survival of this group\textsuperscript{12}.

The UK BASIL-2 trial is randomising CLTI patients between primary IP vein bypass (VB) and best endovascular treatment (BET), which in the UK is predominantly plain balloon angioplasty (PBA), and incorporates a comprehensive cost-utility health economic (HE) analysis\textsuperscript{13,14}. The BASIL prospective cohort study (PCS) is running alongside the main trial and comprises all CLTI patients admitted to The Heart of England Foundation Trust, University Hospitals Birmingham (HEFT UHB) vascular unit between July 2014 and September 2018. The aim of the present study is to calculate and compare, over a 12-month time horizon, the costs of primary IP BS, IP BET, and MLLA in patients enrolled in the BASIL PCS in terms of human and hospital-based resource utilisation in order to inform the BASIL-2 HE analyses.
Patients provided informed, written consent (National Research Ethics Service, Coventry & Warwick, ref: 14/WM/0057). All patients who were admitted to the Heart of England Foundation Trust, University Hospitals Birmingham (HEFT UHB) as an emergency (non elective, unplanned admission) with CLTI (as defined by the Global Vascular Guidelines\(^1\,^2\)) were considered. Only patients with significant peripheral arterial disease that would require revascularisation to vessels distal to, and including the tibioperoneal trunk were recruited. We compared procedural human resource (HR) costs and total in-hospital costs for the index admission and over the following 12-months in 60 consecutive patients undergoing primary IP BS (n=20), IP BET (n=20), or MLLA (10 transfemoral and 10 transtibial) for CLTI. Patients were studied clinically for 12 months after discharge from their index admission using prospectively routinely gathered hospital data. Patients were described in terms of baseline demographics and Wound Ischaemia Foot infection (WIFI) clinical grade to quantify the disease burden of CLTI\(^13\). Amputation Free Survival and Overall Survival were also estimated for each cohort.

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Our hospital is the hub of a vascular network that takes referrals and manages patients with vascular disease from three other local, “spoke” institutions. This covers a population base of over 1.2 million patients. At the time of study, the unit was staffed by 6 vascular surgery consultants. There were 24 dedicated in-patient beds and 4 high dependency beds for patients with vascular disease on the vascular ward. The majority of patients with tissue loss secondary to CLTI are admitted as an emergency from either the outpatient clinic, emergency department or surgical assessment unit. We endeavour to adhere to practice guidelines delineating which patients with CLTI should be managed on an in-patient or out-patient basis as prescribed by the Vascular Society of Great Britain and Ireland\(^14\). We have access to an elective, dedicated vascular operating list for 8 sessions per week (4 full days, 8am to 5pm)
and an emergency theatre (twenty-four hours) which is shared between all surgical specialities. At the time of study our hybrid theatre was not yet commissioned. Interventional radiology access was available from Monday to Friday, 8am till 5pm.

Procedural human resource micro-costing

Procedural human resource (HR) data were collected for each primary intervention from arrival at, to discharge from, the operating theatre or interventional suite. The lead author (MP) attended at the end of each procedure and recorded to the nearest minute the presence of all staff involved. This information was later cross referenced with theatre and interventional radiology electronic records to ensure accuracy. Staff costs (UK£/hour) were obtained from the Personal Social Services Research Unit (PSSRU) (2018). Junior medical staff were assumed to be working a 48-hour working week unless otherwise stated.

The Personal Social Services Research Unit (PSSRU), 2018 document “Unit Costs of Health and Social Care” delineates the average hourly rates of National Health Service (NHS) staff (dependent on grade). Consultant grade doctors (surgeon / anaesthetist / interventional radiologists) cost the NHS £108 per/hour (p/h). The cost of other hospital-based doctors ranges from £24-£105 p/h depending on grade, based on a 56-hour working week. Hospital based nurses, operating department practitioners (ODP) and radiographers all operate under a banding system in the UK NHS system (from 1 to 9) that attracts pay between £28-£123 p/h.

To calculate median costs, exact hourly rates for the type and grade of personnel present were calculated and multiplied by the time, to the nearest minute, that each individual spent at each phase of a procedure. These costs were then combined for each procedure to give the total HR cost for IP BS, BET and MLLA.

Patient level analysis of in-hospital costs
NHS Index Reference Costs (2014/15)\textsuperscript{16} were calculated prospectively from patient level data pertaining to the following:

- index intervention
- index hospital admission: costs for days in hospital were separated into those spent in the ward, high dependency unit (HDU) and intensive care unit (ICU) settings
- further admissions in the 12-months following discharge from the index admission
- further interventions not requiring admission; for example, “day case” BET
- out-patient appointments
- investigations required for diagnosis, treatment and ongoing surveillance
- re-interventions (during the hospital admission and within the following 12-months), any morbidity was described in terms of Clavien-Dindo grade\textsuperscript{17}.

All costs are reported in Sterling (£) rounded to the nearest whole £.

**Statistical Analysis**

Variables were tested for normality using the Shapiro-Wilk test, following which comparisons were performed using either the Mann Whitney U or the Kruskal-Wallis tests. Survival data pertaining to amputation free survival (AFS) and overall survival were calculated using the Kaplan-Meier method and groups were compared using the Log Rank statistic.

The analyses were performed using Jamovi\textcopyright version 1.0.8.0; a graphical user interface based on the R Statistical Package version 3.6.1\textcopyright, The R Foundation for Statistical Computing, 2019. Graphical representations were produced using Prism version 8.3.0, GraphPad\textcopyright 2019.
RESULTS

From the period of 1\textsuperscript{st} June to the 1\textsuperscript{st} of October, 263 patients were entered into the BASIL-PCS (all-comers with CLTI). From this cohort, 60 patients were selected for analysis (20 IP BS, 20 IP BET, 20 MLLA) which represented 22.8\% of the total cohort.

Table I displays the demographics of the populations studied. All three groups were similar in terms of co-morbidity profile, smoking status, obesity, mobility, clinical status, haemodynamic assessment and WIFi clinical grade. More patients who underwent MLLA had undergone previous contralateral limb, above ankle amputation in the past compared to the other two groups.

Procedural details for IP BS and BET can be found in Tables II and III. The majority of bypass patients underwent VB, with only one patient requiring a composite graft (reversed arm vein and PTFE). All grafts were successfully completed at the time of surgery with no immediate failures. All twenty BS cases were completed under general anaesthesia (GA).

One patient in the BS group had a prolonged admission of 127 days and was a clear outlier. Their admission was complicated by significant distal calf wound dehiscence, thrombosis of arteriovenous fistulae for renal dialysis access and urinary tract sepsis requiring admission to a higher level of care. The patient unfortunately died from sepsis during this hospital episode.

Re-interventions were numerous in all cohorts. In the IP BS group, three patients underwent revision surgery to the graft and/or wounds during the index admission. One patient had debridement of an infected groin wound (Clavien-Dindo IIIb). One graft thrombosed within twenty-four hours of surgery and was revised (Clavien-Dindo IIIb). One patient underwent below knee amputation (BKA) in the same admission following graft failure with no other options for revascularisation. In the 12-months following surgery One patient underwent bilateral above knee amputations (AKA) for non-salvageable CLTI. One patient had an inflow angioplasty above the bypass graft for native artery disease. Another two patients had
an outpatient angioplasty of a significant graft stenosis identified by duplex ultrasound surveillance. Two patients had infrainguinal endovascular treatment in the contralateral limb within 12-months of surgery. In total, four patients (20%) underwent repeated revascularisation in the index limb during the study period. All BET cases were performed by a consultant interventional radiologist using local anaesthesia (LA). As is standard practice in the UK, most (90%) had intervention to a single tibial vessel which is usually the least diseased artery. A paclitaxel drug coated balloon (DCB) was used in one case. In two cases it was not possible to cross the target IP lesion. One patient was discharged home for conservative treatment but was re-admitted 2 months later and underwent a BKA. The patient unfortunately died 1 month following this of sepsis secondary to BKA wound ischaemia. The other patient had rest pain only and had successful SFA angioplasty but reestablishment of inline flow via the anterior tibial was unsuccessful. Treatment of the SFA was sufficient to allow the patients management to continue conservatively until the patient’s death in the community 3 years later. No bail out bare metal stents were used in the endovascular cohort. Table II details the vessels treated and technical success rates of the primary interventions only. Subsequent re-interventions were not included. Foot debridement’s were numerous in the BET cohort. Ten debridement’s were performed on 8 patients. Eight of these were considered as primary debridements to remove infected or necrotic tissue following successful IP angioplasty. Two patients returned to theatre for further debridement following a failure to heal, both as inpatients. A further patient had an AKA within 12-months in the index limb. Three patients had repeat infrainguinal endovascular treatment in the index limb during the study period (15%). There were no differences in amputation free survival (AFS) at 12-months (IP BS 75% vs. IP BET 65%, HR 0.88, 95% CI: 0.28 – 2.74, Logrank p=0.82) in those undergoing an attempt at revascularisation (Figure 1).
The majority (85%) of MLLA were performed under GA. Three cases were completed under regional anaesthesia with sedation. There was no significant difference in the total time or HR procedural costs between those undergoing transfemoral or transtibial amputations (Mann-Whitney U, NS).

Patients undergoing MLLA had a longer median pre-intervention in-patient hospital stay (9 days, IQR 3-21) than those undergoing BS (5 days IQR 1-9) or BET (2 days, IQR 0-7) (Kruskal-Wallis, p=.008). Time to intervention was zero for four patients in the BS and eight patients in the BET group who attended for a planned, semi-urgent intervention following out-patient assessment and management. Two of the BET patients were discharged from hospital on the day of intervention, a further three were discharged the following day. The remaining three patients had prolonged stays, requiring in-patient surgical management of tissue loss. In the MLLA group only one patient was admitted on the day of surgery.

There were no significant differences in overall survival (OS) out to 12-months (Logrank p=0.69, figure 2) although OS was somewhat better in those undergoing IP BS (IP BS 80%, IP BET 75%, MLLA 65%). Deaths in the MLLA group were caused by sepsis (2/20), cardiac arrest (2/20), “old age” (1/20), unknown (2/20, community deaths unrecorded in hospital). In the IP BS group mortality was caused by congestive cardiac failure (2/20), mesenteric ischaemia (1/20) and unknown (1/20, community deaths unrecorded in hospital). Finally, in the IP BET group, deaths were due to sepsis (3/20) and unknown (2/20, community deaths unrecorded in hospital).

Procedural HR costs were significantly greater for IP BS than for IP BET or MLLA due to the longer procedural duration and the greater staff requirements, especially where two consultants surgeons were present\textsuperscript{15} (Table IV). Figure 3 shows the spread of HR costs for the three primary interventions. The range of costs for those undergoing BS was much greater than it was for BET or MLLA, largely due to the more variable number of staff and time required to complete each case.
BS was the most intensive in terms of HR requirement. Four cases (20%) required the presence of two consultant surgeons. Consultant surgeon time is the most expensive at £108/hour, trainee surgeon time is somewhat more variable (£24-105/hour, depending on grade). Having two junior level surgeons in theatre for a case is still more likely to be less expensive than one consultant surgeon, given that very few non-consultant grade surgeons attract the higher tariff pay in the UK. If a single consultant surgeon was operating, they were accompanied by two or more junior surgeons for the majority of the operating time (13 cases, 65%). A consultant anaesthetist was present in all 20 BS cases.

The HR requirements for BET were less variable. All cases were performed by one consultant interventional radiologist. A single training doctor of more junior grade was present for only 35% of cases. MLLA was most commonly performed by surgeons of non-consultant grade. A consultant surgeon was present in only four cases (20%). A consultant anaesthetist was present in theatre for all but one MLLA (95%).

Following their index intervention, patients undergoing BET spent less time in hospital (median 1, IQR 1-5, days) than those who received BS (median 8, IQR 4-17, days) or who required MLLA (median 17, IQR 11-28, days), (Kruskal-Wallis, p<.001).

Calculated total hospital costs were significantly greater for MLLA than for either IP BS or IP BET, mainly due to increase length of the index hospital admission (Table IV, Figure 4).

There were no significant differences re-admissions, days spent in hospital, or out-patient appointments in the 12 months following discharge from the index admission (Table V) although total hospital costs still differed significantly (MLLA £26,327, 95% CI: £17,653-30,458 vs. BS £20,401, 95% CI: £12,071-23,926 vs. BET £12,298, 95% CI: £6,961-15,439, p<.001, Kruskal-Wallis) (Figure 5). Although there were no differences in the cost of in-hospital care for MLLA patients compared to those undergoing IP BS this does not include
the considerable costs associated with ongoing community care, rehabilitation, and limb fitting.
DISCUSSION

The present study has found that, over a 12-month time horizon, IP BS is more expensive than IP BET or MLLA in terms of procedural HR costs due the greater requirements for time and staff. This accords with other published data. This was largely due to the presence of more consultant grade staff (at least 2, 1 surgeon, 1 anaesthetist) and assistants required for BS. The range of HR costs of BS was greater than for the other two interventions, probably due to variations in conduit use (arm vein for example) and the location of the distal anastomosis. BS by nature is less predictable and each case presents its own unique challenges. MLLA is much more predictable operation.

Although from a technical perspective, BET can also be unpredictable, the HR costs were more tightly grouped. All cases were performed under LA, by a single consultant interventional radiologist without the requirement of an anaesthetist. Following manual compression, or use of closure device, and adequate haemostasis patients returned directly to the vascular ward without the need for the use of a recovery area. These factors largely explain the lower HR costs for BET.

BET was also the least expensive intervention in terms of hospital costs, which is perhaps unsurprising given that BET is generally quicker to perform and requires less recovery in-hospital. Eight patients (8/20, 40%) underwent planned, semi-elective therapy which was a much higher proportion than those undergoing MLLA or BS.

Patients undergoing MLLA tended to have a prolonged index admission. More timely discharge to “step-down” facilities for on-going care would have reduced the hospital costs associated with the index admission. Also, the lead time from admission to MLLA was relatively long (9 days median) largely due to prior attempts at limb salvage, debridement or drainage of sepsis; or an initial unwillingness on the part of the patient to accept MLLA.
The index hospital admission costs for all three procedures are tightly grouped (Figure 2) except one outlier who underwent BS. This patient had a protracted stay in hospital following a femoro-peroneal bypass with complicated wound sepsis (groin) that required debridement, negative pressure therapy and an intensive care stay with acute renal failure.

Ongoing hospital-based care in terms of outpatient appointments, re-admissions and days spent in hospital in the 12-months following discharge after the index intervention were non-significantly different. Total costs (index admission plus ongoing hospital-based care over 12 months) were greatest for those undergoing MLLA and BS. This was due to the relatively expensive index episodes.

We opted not to individually cost for devices and equipment based on the complexities of health care purchasing in the UK National Health Service (NHS). Each individual NHS hospital trust has contracts with different device manufacturers that are often based on the volume and frequency of use as well as consignment stock. Each hospital trust has its own financial agreement with manufacturers. The financial details of these agreements are usually not disclosed. For these reasons, the cost of devices in our unit may be very different to other hospitals with different device preference and frequencies of use.

There were no pedal bypasses in the IP BS cohort. In recent years, our colleagues have increasingly adopted an endovascular first revascularisation strategy in patients presenting with CLTI. In period from which the current patients were selected (June 2014 to September 2016) 263 patients were admitted to HEFT UHB with CLTI as an emergency (for in-patient care). During this time period, only one popliteal to pedal (dorsalis pedis artery) bypass was performed.

Patients undergoing IP BS had longer delays to treatment than those undergoing IP BET. This is likely to be the case most, if not all, UK vascular units. Patient who require IP BS often require a much more extensive pre-procedural workup in terms of anaesthetic review,
further investigations to delineate fitness for treatment and often more investigations (vein
map, computed-tomography angiography, arterial duplex, digital subtraction angiography)
compared to those undergoing IP BET. In addition, it can be difficult to access sufficient
operating theatre time for often prolonged emergency surgery Again, this is a common
problem right across the NHS.
Costs need to be weighed against patient outcomes and, in particular, data on health-related
quality of life, so that a cost-utility analysis can be used to compare cost-effectiveness of
different treatment strategies. In the UK, The National Institute of Health and Care
Excellence (NICE) use cost per quality of life adjust year (QALY) as a marker of value, with
a current willingness to pay threshold set nationally at £20,000 per QALY. A recent
systematic review into the cost-effectiveness of a BET versus BS strategy for patients with
CLTI secondary to infrainguinal disease reported that BASIL-1 was the only RCT for which
health economic data were available. The Veterans Association study group concluded that
significant, modern evidence was severely lacking to inform healthcare providers and that
future ongoing RCT’s are required to provide this (BASIL-2, BEST-CLI).
Human resource costs are notoriously difficult to estimate, the PSSRU document that we
used to calculate such costs is a standardised format based on average basic salaries. This
does not include any uplifts in pay for extra activity, such as teaching or managerial roles, or
service awards. Although PSSRU HR have been costs may have been an underestimate, it is
the best data source available.

Limitations
The current study estimates costs over a relatively short, 12-month, time horizon and so does
not include the costs of later re-admissions and re-interventions, rehabilitation, limb fitting
and going social care, either at home or in a residential institution.
Rehabilitation services are completely separate from the hospital. Following discharge from hospital, patients with MLLA are usually seen in the outpatient’s department at around 6 weeks to ensure adequate wound healing. If there are no concerns, they are usually discharged from the vascular service.

Although NHS hospital are likely to have very salary and estates costs, we cannot comment formally on the generalisability of our data to other UK vascular units.

Bearing this in mind, and dearth of evidence in the literature regarding the true costs of managing CLTI, further large, multicentre studies are clearly required.

Our aim was to assess the costs of caring for patients with CLTI during their index hospital admission and over the following 12-months. The study was not designed to, and indeed cannot, address the question of the relative long-term clinical and cost-effectiveness of different treatment strategies for CLTI. Only large RCTs such as BASIL-2 and BASIL-3 in the UK and BEST-CLI in the US can address this question. At the time of writing both BASIL-2 and BEST-CLI.

In conclusion, over a 12-month horizon, in terms of calculated procedural HR and in-hospital costs, both IP VB and MLLA are more expensive than IP PBA. Although out to 12 months after discharge from the index admission, the difference in overall hospital costs reduces, it remains significant. These economic data together with QALY data from BASIL-2 will help inform the calculation of incremental cost-effectiveness ratios for different CLTI management strategies.
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