

# Contemporary (2009-2014) clinical outcomes after femoro-popliteal bypass surgery for chronic limb threatening ischaemia are inferior to those reported in the UK Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL) trial (1999-2004)

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1 **Contemporary (2009-2014) clinical outcomes after femoro-popliteal**  
2 **bypass surgery for chronic limb threatening ischaemia (CLTI) are**  
3 **inferior to those reported in the UK Bypass versus Angioplasty for**  
4 **Severe Ischaemia of the Leg (BASIL) trial (1999-2004)**

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## 1 Abstract

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2 **Introduction:** Bypass surgery (BS) remains the “gold standard” revascularisation strategy in  
3 patients with chronic limb threatening ischaemia (CLTI) due to infra-inguinal disease. The  
4 BASIL-1 trial showed that in CLTI patients who survived for 2 years or more, BS resulted in  
5 better clinical outcomes. Despite this, there has been an increasing trend towards an  
6 endovascular first approach to infra-inguinal CLTI. Our aim was to investigate whether  
7 changes in practice have impacted upon the clinical outcomes of BS in our unit ten years  
8 after BASIL-1.

9 **Methods:** Data for patients who underwent femoro-popliteal (FP) BS in BASIL-1 (1999-  
10 2004) were retrieved from trial case record forms. The comparator contemporary series (CS)  
11 comprised all patients undergoing FP BS for CLTI in our unit between 2009-2014.  
12 Demographic and clinical outcome data on CS patients were collected from the  
13 prospectively collected hospital electronic notes. Anatomic patterns of disease in the BASIL-  
14 1 and CS cohorts were scored using Bollinger and GLASS. Statistical analysis was  
15 performed in SAS v9.4.

16 **Results:** There were 128 BASIL-1 and 50 CS patients. Baseline age, gender, affected limb,  
17 and diabetes prevalence were similar, as were days spent in hospital out to 12 months and  
18 length of follow-up. BASIL-1 patients were more likely to be current smokers ( $p=0.000$ ) and  
19 had a higher creatinine ( $p=0.04$ ). The 30-day morbidity and mortality were higher in BASIL-1  
20 (45.3% vs 22%,  $p=0.004$ ). There was no significant difference between BASIL-1 and CS with  
21 regard to run-off Bollinger (37.7 v 32.1,  $p=0.167$ ) and IP GLASS (0 vs 0,  $p=0.390$ ) scores,  
22 with both groups having a median of 2 run-off vessels. Amputation free survival (62% vs  
23 28%, HR 1.86, 95%CI 1.18-2.93,  $p=0.007$ ), limb salvage (85% vs 69%, HR 2.31, 95%CI  
24 1.14-4.68,  $p=0.02$ ), overall survival (69% vs 35%, HR 1.66, 95%CI 1.00-2.74,  $p=0.05$ ) and  
25 Major Adverse Limb Events (67% vs 47%, HR 1.93, 95%CI 1.15-3.22,  $p=0.01$ ) were all  
26 significantly better in BASIL-1.

27 **Conclusion:** Although 30-day mortality and morbidity were significantly lower, all of the  
28 examined longer-term clinical outcomes after FP BS were significantly worse in the CS  
29 group a decade on from BASIL-1. Further research in the form of prospective cohort studies  
30 (PCS) and randomized controlled trials (RCT) is urgently required to determine if the CS  
31 data reported here are generalizable to current vascular surgical practice and, if so, to  
32 determine the reasons for these unexpected outcomes.

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## 1 Introduction

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2 Chronic limb threatening ischaemia (CLTI) is the most severe form of peripheral arterial  
3 disease (PAD) and is characterized by ischemic rest pain and/or tissue loss/gangrene<sup>1,2</sup>. The  
4 worldwide incidence of CLTI is increasing due to ageing and the growing incidence of  
5 diabetes mellitus and chronic kidney disease<sup>3,4</sup>. Despite recent advances in medical  
6 therapies and endovascular, surgical and hybrid revascularisation technologies and  
7 techniques, CLTI patients remain at high risk of cardiovascular mortality and morbidity, and  
8 limb loss<sup>5</sup>. With regard to evidence-based revascularisation (EBR), the first UK NIHR HTA-  
9 funded Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL-1) trial remains  
10 the only published randomised controlled trial (RCT) to have compared a bypass surgery  
11 (BS) first with a plain balloon angioplasty (PBA) first approach to infra-inguinal  
12 revascularisation in CLTI<sup>6</sup>. BASIL-1 showed that in patients likely to live for more than two  
13 years, overall (OS) and amputation free survival (AFS) were better following randomization  
14 to BS than to PBA. Despite this 'level 1' evidence in favour of BS over PBA, there has been  
15 a world-wide trend towards an endovascular first approach to the treatment of femoro-  
16 popliteal (FP) disease in patients with CLTI. Those advocating such an approach point to  
17 lower peri-procedural morbidity and mortality, and further claim that current best  
18 endovascular treatment (BET) results in far superior outcomes than those reported in  
19 BASIL<sup>7-9</sup>. Although not evidence-based, in many vascular units around the world, BS is  
20 increasingly reserved for those patients who cannot have endovascular intervention or  
21 where such intervention has failed. Due to the lack of published contemporary series (CS)  
22 of BS for CLTI, the impact of such practice on outcomes following BS is unknown. The aim  
23 of the present study, therefore, is to compare clinical outcomes following FP BS in a CS  
24 (2009-2014) from a single UK academic vascular unit with those reported in the BASIL-1 trial  
25 operated a decade earlier (1999-2004).

26

## 1 **Methods**

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2 The BASIL-1 trial randomised 452 patients presenting with CLTI due to infra-inguinal  
3 disease to either a BS-first or a PBA-first revascularisation strategy. The recruitment period  
4 was 1999 to 2004 and follow up ended on 1 July 2007<sup>10</sup>. For the present analysis, the  
5 BASIL-1 cohort comprised trial patients undergoing primary FP BS with any conduit. The CS  
6 cohort comprised patients undergoing primary FP BS for CLTI with any conduit in our unit  
7 between 2009 and 2014 and follow-up ended on 31 May 2017. Within the CS study period  
8 (2009-2014), 132 FP BS were performed in our unit. Of these, 72 BS were for claudication  
9 (IC) or popliteal aneurysm disease and so were excluded; as were four contralateral BS and  
10 six secondary BS performed for failed endovascular interventions within the previous 12  
11 months. This left 50 patients in the CS cohort undergoing primary FP BS for CLTI compared  
12 with 128 BASIL-1 patients.

13 The BASIL-1 and CS cohorts were compared in terms of baseline factors, 30-day mortality  
14 and morbidity, length of hospital stay out to 12 months and amputation-free survival (AFS),  
15 limb salvage (LS), overall survival (OS), and freedom from re-intervention (FFR) and major  
16 adverse limb events (MALE). FFR was defined as the absence of subsequent re-  
17 vascularization or intervention for any post-operative complications. Minor amputations were  
18 excluded as they were considered a consequence of the clinical presentation. Major  
19 amputation was defined as amputation above the ankle joint. Minor amputation includes  
20 amputation of single or multiple digits, or trans-metatarsal amputation (no Chopart's or  
21 Lisfrank amputations were performed within the trial). MALE was defined as any ipsilateral  
22 limb intervention (excluding minor amputation) after initial intervention. Bollinger<sup>11</sup> and Global  
23 Vascular Guideline (GVG) GLASS grade and scores were used to quantify the pattern of  
24 anatomical disease prior to intervention.

25 GLASS score is a new anatomical staging system designed by an expert global panel as  
26 part of the Global Vascular Guidelines on Chronic Limb Threatening Ischaemia. GLASS is  
27 part of the Patient, Limb, Anatomy paradigm presented in the GVG. GLASS involves  
28 choosing the target artery pathway (TAP) for endovascular revascularisation from the origin  
29 of the SFA (common and deep femoral disease are considered part of "inflow" and  
30 considered corrected prior to more distal revascularisation) to the foot with the aim of  
31 establishing in-line flow. Disease severity in FP and IP segments are graded separately on  
32 features including length of disease, stenosis or occlusion and level of calcification. FP and  
33 IP grades are combined within a matrix to determine GLASS stage. GLASS stage is  
34 believed likely to correlate with endovascular immediate technical success rates and 12-

1 month limb-based patency (LBP) GLASS has been presented at the European Society of  
2 Vascular Surgery, Lyon (France) 2017, and Society of Vascular Surgery VAM in San Diego  
3 (2017) and Boston (2018). The concept is that GLASS will act as an aid to shared-decision  
4 making and stratification within trials comparing different form of revascularisation. We  
5 understand that the the GVG on CLTI are likely to be published in EJVES and JVS  
6 supplement in Q4 of 2108.

7 Ethical approval was granted for the BASIL trial (ISRCTN – 45398889), no ethical approval  
8 was required for the CS data collection as this is classed as audit of clinical outcomes.

9 Hazard ratios were used to detect statistically important differences in outcomes using 95%  
10 confidence intervals. Differences between the cohorts were compared using t-test, chi-  
11 squared and Wilcoxon Rank Sum tests according to distribution of data. Statistical analysis  
12 was performed using SAS v 9.4.

13

## 1 Results

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2 Patient age, gender, and prevalence of diabetes were similar in both cohorts. BASIL patients  
3 were more likely to be current smokers, less likely to be on best medical therapy (BMT), and  
4 had a higher baseline creatinine (**Table 1**). Immediate technical success rate, as judged by  
5 the operating surgeon, was very high in both the BASIL-1 (126/128, 98%) and CS (50/50,  
6 100%) cohorts. Minor amputation rates were equivalent between the two cohorts (23.4% vs  
7 20%,  $p=0.6$ ) suggesting equivalent burden of tissue loss. BASIL-1 trial patients had a non-  
8 significantly longer mean (SD) index admission when compared to the CS patients (23.2  
9 [26.3] vs 15.6 [20.3] days,  $p = 0.7$ ). However, difference in cumulative inpatient hospital days  
10 by 12 months had virtually disappeared (24.2 [26.4] versus 27.3 [26.8] days,  $p = 0.5$ ).  
11 BASIL-1 patients suffered significantly higher overall combined peri-operative (30-day)  
12 mortality and morbidity (45% vs 22%;  $p = 0.004$ ), including higher rates of wound infection  
13 ( $p=0.02$ ). However, there was no significant difference in major adverse cardiac events  
14 (MACE) (8% vs 2%,  $p=0.1$ ) (**Table 2**). With regard to long-term clinical outcomes, AFS (62%  
15 vs 28%, HR 1.86, 95% CI 1.18-2.93,  $p=0.007$ ), LS (85% vs 69%, HR 2.31, 95% CI 1.14-  
16 4.68,  $p=0.02$ ), OS (69% vs 35%, HR 1.66, 95% CI 1.00-2.74,  $p=0.05$ ) and MALE (67% vs  
17 47%, HR 1.93, 95% CI 1.15-3.22,  $p=0.01$ ) were all significantly better in the BASIL-1 cohort  
18 (**Figures 1-4**). FFR (76% vs 60%, HR=1.70, 95% CI 0.88 – 3.27,  $p=0.1$ ) was non-  
19 significantly better in BASIL-1 when compared to the CS cohort (**Figure 5**). In terms of  
20 anatomic burden of disease, there was no significant difference between BASIL-1 and CS  
21 with regard to run-off Bollinger score (37.7 vs 32.1,  $p=0.167$ ) and IP GLASS (0 vs 0,  
22  $p=0.390$ ) grade, with both groups having a median of 2 run-off vessels. Nor was there any  
23 difference between total Bollinger score (63.1 vs 65.4,  $p=0.926$ ). However, patients in the  
24 CS had a significantly higher FP GLASS score (3 vs 4,  $p=0.000$ ) (**Table 3**).

25

## 1 Discussion

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2 In the present study, although peri-operative (30-day) mortality and morbidity were  
3 significantly lower, long-term clinical outcomes following primary FP BS for CLTI in our unit  
4 between 2009 and 2014 were significantly worse than those reported in the BASIL-1 trial a  
5 decade earlier (1999-2004). Further research is required to determine if the CS data  
6 reported here are generalizable to current vascular surgical practice and, if so, to determine  
7 the reasons for these unexpected data. Possible causes include a loss of surgical skills as a  
8 result of the overall reduction in open vascular procedures and/or a tendency to reserve BS  
9 for patients considered unsuitable for endovascular intervention due the severity of their  
10 tissue loss and/or the extent and complexity of their underlying disease<sup>12-15</sup>. While loss of  
11 surgical skills is certainly possible, this does not appear to be supported by the observation  
12 that CS patients had lower overall 30-day mortality and morbidity as well as a trend towards  
13 a shorter index admission<sup>16-19</sup>. With regard to the clinical severity of disease, the proportion  
14 of patients with tissue loss was similar in the two cohorts. We were unable to determine the  
15 extent of tissue loss in the CS patients with same precision as was the case in BASIL-1.  
16 However, using rates of minor amputation as a surrogate, it would seem that the severity of  
17 tissue loss was broadly similar in both groups. With regard to anatomic complexity of  
18 disease, the Bollinger scoring and GLASS grade would suggest a similar disease burden.  
19 Importantly the run off scores were almost identical for both groups suggesting that the  
20 outflow for bypass surgery was equivalent. Post procedural surveillance may have been  
21 different between the two cohorts. Surveillance post bypass was not prescriptive in BASIL-  
22 1, its use was not recorded and re-intervention was largely clinically driven. In the CS only  
23 15 patients were enrolled in formal ultrasound graft surveillance, none had formal  
24 haemodynamic surveillance. As such, it is possible that differences in post bypass care  
25 could contribute to the difference in clinical outcomes observed.

26 An important question is the degree to which our practice and the outcomes reported here  
27 can be generalized more widely to current vascular and endovascular practice within the UK  
28 and elsewhere. Like many units, despite a lack of evidence indicating that endovascular  
29 intervention offers a more clinically effective and cost-effective option for CLTI patients who  
30 could have a vein bypass, and growing evidence that failed endovascular intervention  
31 compromises outcomes following subsequent BS, we have increasingly employed an  
32 endovascular first approach to the management of CLTI. Thus, during the study period  
33 (2009-2014), almost five times more (n = 237) patients had a FP endovascular intervention  
34 for CLTI than had BS (n = 50). In the UK, virtually all CLTI patients are managed within the  
35 National Health Service (NHS), where care is provided free at the point of delivery to all UK



1 and European Union citizens, by salaried vascular surgeons and interventional radiologists.  
2 As such, the “turf battles” and re-imburement issues seen elsewhere in the world are  
3 largely irrelevant to UK practice. Rather, the main reason for our endovascular preference is  
4 probably a reluctance to subject elderly and co-morbid patients to prolonged surgery and,  
5 linked to that, a belief that an endovascular approach is associated with less resource  
6 utilization in terms of operating theatre time and bed days in hospital. However, these beliefs  
7 are not supported by hard data and we have to accept that our current practice may not be  
8 maximizing long-term clinical outcomes for the greatest number of our CLTI patients.

9 Interestingly, in the UK, Heikkila et al.<sup>20</sup> have recently published 1-year outcomes following  
10 lower limb revascularisation using data from the national vascular registry (NVR), hospital  
11 episode statistics (HES), and the office of national statistics (ONS). The authors conclude  
12 that overall survival and amputation rates have significantly improved over a 10-year period.  
13 They suggest that one reason for the observed improvement may be centralization of  
14 services due to increased specialization in vascular surgery. These UK national data would  
15 seem to starkly contradict those reported here from a single UK academic vascular unit.  
16 However, it must however be noted that Heikkila and colleagues grouped together a wide  
17 range of surgical and endovascular procedures, studies patients with CLTI and intermittent  
18 claudication (IC), and that their follow-up was short. Unfortunately, at the present time, there  
19 are very few other published data with which we can compare our own long-term outcome  
20 data. Thus, most surgical and endovascular CLTI cohorts reported in the literature have  
21 limited follow-up and/or mix CLTI with IC and/or mix FP with infra-popliteal (IP) procedures  
22 which makes interpretation of the data extremely difficult<sup>21-23</sup>.

23 In summary, therefore, there is a clear and urgent need to perform further RCTs to  
24 determine the pros and cons of a BET-first versus a BS-first revascularisation strategy in  
25 sub-groups of CLTI patients presenting with different degrees of tissue loss and anatomic  
26 complexities of disease. To this end, in the UK, NIHR HTA is funding the BASIL 2<sup>24</sup> and  
27 BASIL 3<sup>25</sup> to inform practice in IP disease and the impact of drug eluting technologies in the  
28 FP segment respectively. In the US, NIH have funded the BEST-CLI<sup>26</sup> trial. Together, these  
29 on-going trials will report contemporary clinical outcomes in several thousand patients  
30 undergoing BET and BS for CLTI and inform EBR decisions going forward.

## 31 **Conclusion**

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33 Although 30-day mortality and morbidity were significantly lower, all of the examined longer-  
34 term clinical outcomes after FP BS were significantly worse in the CS group a decade on  
35 from BASIL-1.



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