Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial

*BASIL trial participants**

Summary

Background The treatment of rest pain, ulceration, and gangrene of the leg (severe limb ischaemia) remains controversial. We instigated the BASIL trial to compare the outcome of bypass surgery and balloon angioplasty in such patients.

Methods We randomly assigned 452 patients, who presented to 27 UK hospitals with severe limb ischaemia due to infra-inguinal disease, to receive a surgery-first (n=228) or an angioplasty-first (n=224) strategy. The primary endpoint was amputation (of trial leg) free survival. Analysis was by intention to treat. The BASIL trial is registered with the National Research Register (NRR) and as an International Standard Randomised Controlled Trial, number ISRCTN45398889.

Findings The trial ran for 5·5 years, and follow-up finished when patients reached an endpoint (amputation of trial leg above the ankle or death). Seven individuals were lost to follow-up after randomisation (three assigned angioplasty, two surgery); of these, three were lost (one angioplasty, two surgery) during the first year of follow-up. 195 (86%) of 228 patients assigned to bypass surgery and 216 (96%) of 224 to balloon angioplasty underwent an attempt at their allocated intervention at a median (IQR) of 6 (3–16) and 6 (2–20) days after randomisation, respectively. At the end of follow-up, 248 (55%) patients were alive without amputation (of trial leg), 38 (8%) alive with amputation, 36 (8%) dead after amputation, and 130 (29%) dead without amputation. After 6 months, the two strategies did not differ significantly in amputation-free survival (48 *vs* 60 patients; unadjusted hazard ratio 1·07, 95% CI 0·72–1·6; adjusted hazard ratio 0·73, 0·49–1·07). We saw no difference in health-related quality of life between the two strategies, but for the first year the hospital costs associated with a surgery-first strategy were about one third higher than those with an angioplasty-first strategy.

Interpretation In patients presenting with severe limb ischaemia due to infra-inguinal disease and who are suitable for surgery and angioplasty, a bypass-surgery-first and a balloon-angioplasty-first strategy are associated with broadly similar outcomes in terms of amputation-free survival, and in the short-term, surgery is more expensive than angioplasty.

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Introduction

In most developed countries, the incidence of severe limb ischaemia, which is the presence of tissue loss (ulceration, gangrene) and pain at rest or at night, is estimated to be 50–100 per 100 000 every year and leads to pronounced morbidity and mortality as well as to the consumption of many health-care and social-care resources.[1] Ageing populations, the increasing prevalence of diabetes and its lower-limb-related complications, and the failure thus far to substantially reduce tobacco consumption, mean that despite advances in medical therapies, the numbers of patients needing lower limb revascularisation for severe limb ischaemia will probably increase in the foreseeable future.[2,3]

Two treatments are currently available; bypass surgery and balloon angioplasty. Those who favour surgery usually emphasise good long-term anatomical patency and clinical durability.[4–6] However, this preference could come at the cost of high morbidity and mortality as well as substantial resource use.[7] Furthermore, this durability could depend heavily on routine ultrasonography-based graft surveillance, often leading to repeated prophylactic re-interventions, and the use of good-quality veins for grafting.[8,9] Unfortunately, adequate vein is often unavailable and the long-term results of bypasses constructed with prosthetic materials are much less satisfactory.[4,10] By contrast, proponents of balloon angioplasty point to the advantages of low procedural morbidity and mortality, reduced costs, the speed with which the procedure can be undertaken, and a shortened hospital stay.[11] Furthermore, supporters will claim that failed angioplasty does not jeopardise subsequent surgery and that, unlike bypass surgery, it preserves collaterals so that even if the angioplasty site occludes, symptoms might not return.[11–13] Apart from the limited patency of angioplasty, critics will state that only a few patients may be suitable for use of the transluminal technique, and that although a subintimal approach could increase applicability, the procedure is so technically demanding in these patients that satisfactory results might not be widely achievable.[14–19]

However, these differing opinions are based on little or no evidence. In previous studies[6,20–24] that have attempted to compare surgery and angioplasty for various degrees of lower limb ischaemia, all had one or more major methodological problems.[16,18–21,25–32]

The complete absence of level 1 evidence leads to controversy as to which treatment is associated with better clinical outcome and more effective use of health-care resources in patients with legs threatened by severe limb ischaemia and who are potentially suitable for both treatments.[33–39] Our aim in the BASIL (bypass versus angioplasty in severe ischaemia of the leg) trial was to compare the outcomes of a surgery-first strategy with an angioplasty-first strategy in patients with severe limb ischaemia.

Methods

Patients and procedures

The BASIL trial methods have been published elsewhere.[40] Briefly, consultant vascular surgeons and interventional radiologists in participating centres were asked to consider all patients who had presented to them with severe limb ischaemia, defined as rest pain or tissue loss (ulcer or gangrene) of presumed arterial aetiology for more than 2 weeks, and who on diagnostic imaging had a pattern of disease which, in their joint opinions, could equally well be treated by either infra-inguinal bypass surgery or balloon angioplasty. All patients provided written informed consent, and the study was approved by the multicentre research ethics committee for Scotland.

Recruitment began in August, 1999, and finished in June, 2004, during which time 452 patients underwent randomisation at one of 27 UK hospitals. Data were collated centrally and confidentially at the trial office. The trial manager, independent of participating centres, randomly assigned patients to receive either surgery first or angioplasty first using a one-to-one ratio in randomly sized permutated blocks. The randomisation sequences were generated by a computerised random-number generator in the University of Edinburgh Medical Statistics Unit (Edinburgh, UK) and supplied to the coordinating centre in identical, sealed envelopes. Randomisation was stratified by centre, and then into four groups by clinical presentation (rest pain only *vs* tissue loss with or without rest pain) and ankle pressure ($\geqslant$50 mm Hg *vs* $\leqslant$50 mm Hg).[41,42]

Centres were encouraged to undertake the allocated procedure as soon as possible after randomisation. The responsible consultant vascular surgeons and interventional radiologists were allowed to use their preferred techniques and equipment for diagnosis and treatment. With respect to imaging, more than 95% of the patients underwent diagnostic angiography before being allocated to receive either surgery or angioplasty. We obtained follow-up data prospectively by research nurses based in the main recruitment centres and allocated to other centres in the same UK region.

Details of patients recruited in Scottish centres were logged with the Information and Statistics Division (ISD) of the National Health Service in Scotland. Notification of death, interventions, and discharges from hospital to the end of the trial were provided by record linkage with Scottish Morbidity Records (SMR01) and General Registrar Office Scotland (GRO[S]) death records. We obtained similar information for patients from English centres using patients' reported information that was checked through hospital paper records, hospital electronic information systems, and family practitioners. Additionally, this prospectively gathered information was crosschecked by review of all available (435 of 452) hospital case notes of trial patients at the end of the study.

Our primary outcome was time to amputation of the trial leg above the ankle or death from any cause, whichever occurred first (ie, amputation-free survival). Secondary outcomes were all-cause mortality, 30-day morbidity and mortality, re-interventions, health-related quality of life (HRQL), and use of hospital resources.

We audited the proportion of patients assigned into BASIL with respect to the total population of patients presenting with severe limb ischaemia, and investigated the reasons for non-interventional treatment and non-randomisation of potentially eligible patients. From October, 2001, to April, 2002 (about halfway through the recruitment period), we prospectively obtained data for all consecutive patients who presented with severe limb ischaemia, and who subsequently underwent diagnostic imaging with a view to revascularisation by either surgery or angioplasty, at one of the top six recruiting centres (by number of patients recruited). The responsible consultant vascular surgeons and interventional radiologists were asked to jointly record the reason why, in their opinion, potentially eligible patients were not suitable for revascularisation or randomisation.

An independent data monitoring committee met every 6 months during randomisation. The stopping rule was the observation of a highly significant difference in the primary endpoint between the treatment groups ($p<0{\cdot}001$). The data monitoring committee made recommendations to the steering committee on whether the trial should continue and on the nature and the quality of the data being collected. No one apart from the data monitoring committee and independent statisticians who analysed and prepared the data had access to these analyses.

We measured self-reported HRQL using the EuroQoL 5-D (EQ5D)[43] and short form 36 (SF36).[44] These generic measures were recorded at baseline and at 3, 6, and 12 months after randomisation. The EQ5D responses were converted into a single weighted utility (preference based) score by use of the original time trade-off tariff set.[45] We combined the SF36 items into physical and mental component summary scores using recommended procedures.[46] For all three measures, higher scores indicate better health and wellbeing as perceived by the patient. Unadjusted differences in mean EQ5D weighted scores and SF36 component summary scores were assessed by simple linear regressions. Adjusted differences allowing for baseline scores were based on bias-corrected matching estimators.[47]

We obtained data for all interventions and hospital stays during follow-up. Patients' specific hospital use was measured by the duration of hospital stay as an aggregate unit of services provided in the inpatient hospital setting. Total length of hospital stay was measured for 1 year from the date of randomisation. We estimated hospital use costs, by using the Scottish system of hospital cost statistics for the average cost per inpatient day.[48]

Statistical analysis

The sample size calculations proposed that 223 patients per treatment would be needed for a 90% power to detect a 15% difference in 3-year amputation-free survival at the 5% significance level. This calculation was based on the assumption that the 3-year survival value might be 50% in one group and 65% in the other.

We undertook the statistical analysis according to a predefined protocol. Kaplan-Meier methods were to be used to construct survival curves on an intention-to-treat basis, with the date of randomisation as time zero. Survival to the primary endpoint and a secondary endpoint (all-cause mortality) were compared by intention-to-treat analysis. We compared treatments by using mean survival to these two endpoints at 1 and 3 years from randomisation and mean values of hazard rates using a Cox model. The hazard rates were to be compared between treatments during the entire follow-up period, and calculated separately for those events occurring between randomisation and 6 months and those occurring after 6 months, and were to be adjusted for a predefined set of covariates. Covariate interactions with treatment were examined for three specified covariates (clinical stratification group, and diabetes and creatinine above or below the median) and also for a hazard score calculated from covariates that classified patients according to their risk of experiencing an endpoint. All cleaning and checking of the follow-up data were done without reference to the allocated treatment. After the survival curves were examined, a further post-hoc analysis was done that compared the risks of endpoints occurring between randomisation and 2 years and occurring after 2 years. The BASIL trial is registered with the National Research Register (NRR) and as an International Standard Randomised Controlled Trial, number ISRCTN45398889.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for decision to submit for publication.

Results

During the 6-month BASIL audit, 585 consecutive patients presented with severe limb ischaemia to the top six recruiting centres (which between them recruited 61% of the patients entered into the trial) and underwent diagnostic imaging, usually angiography, with a view to revascularisation by surgery or angioplasty. Of these, 129 (22%) needed supra-inguinal (aorto-iliac) intervention and were therefore not the subject of the trial. Of the remaining 456 patients with severe limb ischaemia due to infra-inguinal disease (272 men, 184 women, median age 75 years [IQR 67–82]), 220 (48%) were treated without revascularisation and 236 (52%) underwent revascularisation. Of these 236 potentially eligible patients, 70 (29%) were regarded as suitable for randomisation into BASIL; of these, 22 (31%) refused trial entry and 48 (69%) were randomised.

In the audit, the main reason (more than one reason was given in many instances) for responsible surgeons and radiologists not revascularising or not randomly assigning the remaining 386 patients was that the leg could not be revascularised by either surgery or angioplasty in 154 (34%). Additionally, there was clinically significant comorbidity precluding surgery in 34 (7%) patients, there had been symptomatic improvement with

	Balloon angioplasty first (n=224)	Bypass surgery first (n=228)
Male sex	128 (57%)	141 (62%)
Age		
<70 years	67 (30%)	80 (35%)
70–79 years	104 (46%)	89 (39%)
≥80 years	53 (24%)	59 (26%)
Right leg used as trial leg	103 (46%)	99 (43%)
Smoking status		
Never smoked	48 (21%)	41 (18%)
Current smoker	72 (32%)	92 (40%)
Ex-smoker (not smoked for more than 1 year)	104 (46%)	95 (42%)
Diabetes		
Not known to have diabetes	129 (58%)	133 (58%)
Insulin-dependent	39 (17%)	39 (17%)
Non-insulin-dependent	56 (25%)	56 (25%)
Angina	42 (19%)	41 (18%)
Previous myocardial infarction	44 (20%)	35 (15%)
Previous stroke or transient ischaemic attack	40 (18%)	57 (25%)
Previous intervention in trial leg	40 (18%)	27 (12%)
Previous intervention in other leg	36 (16%)	47 (21%)
Symptomatic arterial disease in other leg?		
No	151 (67%)	145 (64%)
Yes: intermittent claudication*	21 (9%)	24 (11%)
Yes: severe limb ischaemia	52 (23%)	59 (26%)
Pain at rest or at night only in trial leg	207 (92%)	205 (90%)
Tissue loss (ulcer or gangrene) in trial leg	169 (75%)	167 (73%)
Randomisation stratification group		
A: pain at rest and at night only; ankle pressure ≥50 mm Hg	45 (20%)	48 (21%)
B: pain at rest and at night only; ankle pressure <50 mm Hg	10 (4%)	13 (6%)
C: tissue loss with or without pain at rest and at night; ankle pressure ≥50 mm Hg	108 (48%)	114 (50%)
D: tissue loss with or without pain at rest and at night; ankle pressure <50 mm Hg	61 (27%)	53 (23%)
On a statin†	77 (34%)	75 (33%)
On drug treatment for hypertension	141 (63%)	134 (59%)
On antiplatelet drug‡	120 (54%)	141 (62%)
Creatinine concentration (μmol/L, mean [SD])	113 (62)	116 (95)

Data are number (%) unless otherwise stated. *Pain in leg when walking but not at rest or at night, no tissue loss. †For hypercholesterolaemia. ‡In most cases, aspirin 75 mg daily.

Table 1: **Baseline characteristics of trial patients**

	During same hospital stay as first intervention		Following discharge from hospital after first intervention	
	Angioplasty (n=237)	Surgery (n=197)	Angioplasty (n=230)	Surgery (n=186)
Mortality	7	11	0	0
Morbidity				
Angina	4	4	1	2
Myocardial infarction	6	13	2	2
Stroke	1	3	2	0
Haematoma (numbers needing surgical drainage)	16 (2)	19 (9)	1 (0)	5 (0)
Wound infection	18	45	25	29
Chest infection	4	10	3	2
Urine infection	8	7	2	6
False aneurysm (numbers needing surgical repair)	0 (0)	2 (1)	0 (0)	0 (0)
Venous thromboembolism	1	0	2	0
Other	2	2	8	9
Further interventions				
Angioplasty	3	1	1	0
Surgery	21	2	13	0
Amputation of trial leg				
Above/below knee	4/5	3/3	0/1	0/0
Partial foot or toe	11	11	2	2
Graft re-exploration	0	5	0	0
Embolectomy	1	2	1	0
Thrombectomy	0	3	0	1
Wound debridement	3	6	1	1
Other (non-vascular)	0	0	0	1

Data are number of individuals. Patients could have had more than one morbidity or re-intervention event both before and after discharge, but within 30 days.

Table 2: **Mortality, morbidity, and re-interventions within 30 days after first intervention**

medical therapy only in 14 (3%), patients were unable to provide informed consent in 16 (4%), and the patient's pattern of disease was technically unsuitable for angioplasty in 75 (16%) or surgery in 93 (20%).

For the BASIL trial as a whole, 452 patients from 27 hospitals entered the trial. The assigned interventions were attempted for 195 (86%) of 228 patients assigned to surgery at a median of 6 days (IQR 3–16) and for 216 (96%) of 224 assigned to angioplasty at 6 days (2–20; no significant difference in time to attempt). The baseline characteristics of the patients in each group were similar and typical of those presenting with severe limb ischaemia (table 1). More than 40% were known to have diabetes and more than a third were current smokers. Most patients had tissue loss and a quarter had both legs affected by severe limb ischaemia. Many of the patients were elderly and most had a previous history of clinically significant cardiovascular disease. Despite this high occurrence, a third of patients were not receiving an antiplatelet drug and only a third of patients were receiving a statin. 33 patients were prescribed warfarin, with roughly equal numbers in the two groups.

Seven (2%) individuals (three assigned angioplasty, four surgery) were lost to follow-up after randomisation; but only three (one, two) were lost during the first year of follow-up. By the close of follow-up on Feb 28, 2005, 449 (99%) patients had been followed up at 1 year, 336 (74%) at 2 years, 216 (48%) at 3 years, 99 (22%) at 4 years, and 37 (8%) at 5 years. Follow-up finished once the patient had reached an endpoint (amputation of trial leg above the ankle or death). At the end of follow-up, 248 (55%) patients had not reached the primary endpoint (ie, were alive with their trial leg intact), 38 (8%) were alive with their trial leg amputated, 36 (8%) had died subsequent to having their trial leg amputated, and 130 (29%) had died without amputation (with their trial leg intact).

Six patients randomly assigned to surgery and one to angioplasty died before undergoing intervention. 11 (5%) patients randomised to surgery and seven (3%) to angioplasty died within 30 days of their first intervention (non-significant difference). One patient in each randomised group crossed over and died within 30 days of the alternate procedure, so that the 30-day mortality associated with each procedure is the same, whether analysed by intention to treat or by first treatment received. 110 (56%) of 195 patients who were assigned to and underwent attempted surgery as their first procedure and 89 (41%) of 216 patients who were assigned to and underwent attempted angioplasty as their first procedure had one or more complications within 30 days of their intervention. However, of these 89 patients, 20 did not develop their complication until after they had gone on to have surgery as a second procedure after a failed angioplasty as a first procedure.

Table 2 describes the 30-day mortality, morbidity, and re-interventions after the first procedure, irrespective of the treatment to which they were initially allocated, and distinguishes events that occurred during the same hospital stay and those that occurred after discharge. Although we recorded no significant difference in mortality, surgery was associated with a significantly higher rate of early morbidity (110 [57%] of 194) than the rate with angioplasty (89 [41%] of 216; difference 15·5%, 95% CI 5·8–24·8); these morbidity events being mainly infective, wound, and cardiovascular complications.

Of the 228 patients assigned to receive surgery, 195 underwent attempted surgery (figure 1). Of these patients, five underwent a successful endarterectomy and vein patch rather than a bypass. Two bypasses were abandoned; one because the surgeon judged the vessels as too calcified to construct a distal anastomosis, and one because the surgeon could not find sufficient usable vein for a conduit and did not want to use a prosthetic graft. In a further three patients, a graft was inserted and the operation completed but, in the opinion of responsible consultant surgeon undertaking the procedure, the bypass was not working at the end of the procedure. Therefore, the immediate failure rate was 3% (five of 195). Thus, 193 (85%) patients allocated to surgery underwent a completed surgical procedure as their first intervention, of which 188 were completed bypasses. Of these bypasses, 177 (94%) originated from the femoral

artery and 141 (75%) were constructed using the patient's long saphenous vein. About a third of the distal anastomoses were constructed at each of the following sites: above-knee popliteal artery, below-knee popliteal artery, and crural arteries (anterior or posterior tibial or peroneal arteries).

Additionally, four patients who had been assigned to angioplasty underwent successful bypass surgery as their first intervention. By 12 months, 85 of 195 with attempted surgery had resulted in clinical failure defined by death, major amputation, or a return or persistence of symptoms (rest pain, tissue loss) in the trial leg or the finding of a technical problem with the graft on surveillance. Of the patients with a return of symptoms, 33 had a second intervention (angioplasty in most patients). Figure 1 details the outcomes of these patients undergoing further interventions, within 12 months of randomisation (web-figures 1 and 2 show further outcomes and interventions of each strategy).

Of the 224 patients allocated to receive angioplasty, 216 underwent attempted angioplasty (figure 1). 43 (20%) of these procedures were judged as immediate technical failures. In ten, the vessel lumen could not be entered or the lesion could not be completely crossed with a guide wire. In 18, the lesion was crossed subintimally but the lumen could not be re-entered. Two procedures were abandoned before a guide wire had been passed across the disease because the patients could not tolerate the procedure. Two were terminated because of vessel perforation after a guide wire had been passed. One was terminated immediately because the lesion that had been described as being present on pre-operative duplex ultrasonography was found not to be present at the time of angiography. In a further ten procedures, immediate thrombosis of the angioplasty channel occurred, of which six also had distal embolisation, which could not be rectified either by thrombolysis or aspiration.

Of the 203 attempted angioplasties in which a guide-wire was passed across at least part of the lesion to be treated, 36% were transluminal, 50% were subintimal, and 14% were mixed. The superficial femoral artery was treated in 162 (80%) patients, and in 126 (62%) patients, more distal vessels also underwent angioplasty. Thus, the extent of the lesion that had been bypassed at surgery and recannalised by angioplasty was similar.

Furthermore, 21 patients allocated to surgery crossed over and underwent attempted angioplasty as their first intervention; of these, five were immediate failures. By 12 months, 109 of 216 patients given attempted angio-plasty had resulted in clinical failure. Of these, 59 went on to have a second intervention, which in most instances was surgery.

After randomisation to surgery and attempted treatment, 109 (56%) of 195 patients were alive with the trial leg intact at 12 months without further intervention. This value compares with 107 (50%) of 216 patients after randomisation to angioplasty and attempted treatment. With respect to an intention-to-treat analysis, surgery was associated with a lower re-intervention rate than angioplasty (41 [18%] of 224 *vs* 59 [26%] of 228; difference 8%, 95% CI 0·04–15%). With analysis by the first intervention received, the difference between re-intervention after surgery and angioplasty increases (33 [17%] of 199 *vs* 67 [28%] of 237; 11%, 4–19%).

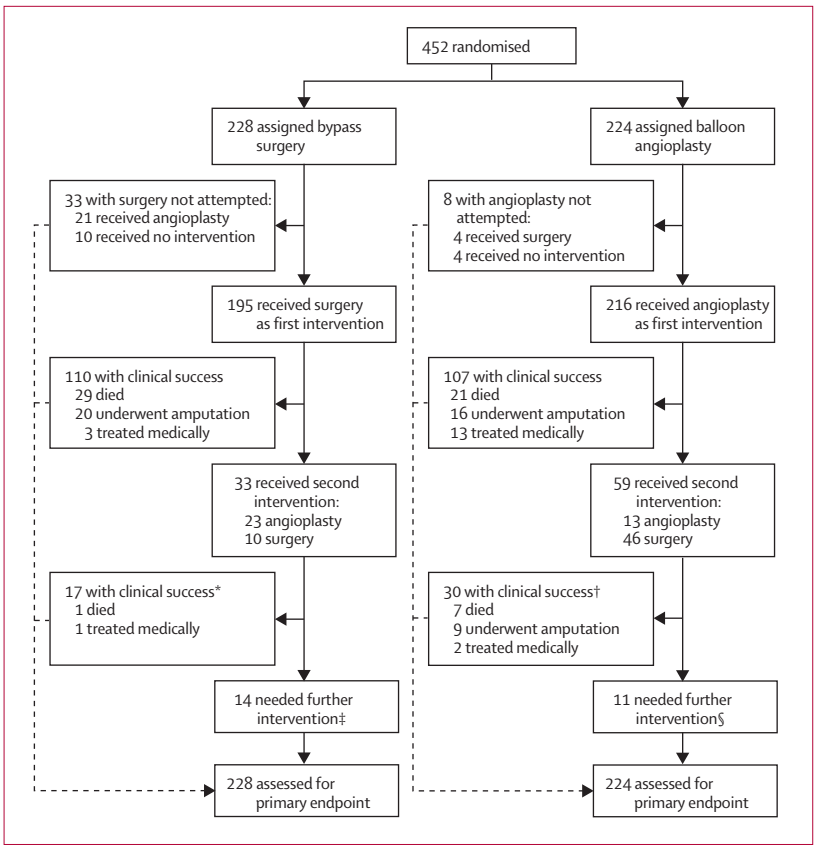

Figure 1: **Trial profile at early (12-month) follow-up**
*Three patients after surgery, 14 after angioplasty. †21 after surgery, nine after angioplasty. Seven after surgery, seven after angioplasty. §Nine after surgery, two after angioplasty.

See Lancet Online for webfigures 1 and 2

Figures 2 and 3 are Kaplan-Meier survival curves showing time to amputation of trial leg or death (whichever came first) and time to death from any cause. Survival to the primary endpoint (amputation-free survival) at 1 year was 68% and at 3 years was 57% for those assigned to surgery first; survival at 1 year was 71% and at 3 years was 52% for those randomised to angioplasty first. There were no significant differences in survival to either endpoint by randomised group. Table 3 shows hazard ratios (HR) comparing randomised treatments by Cox proportional hazards. None of the planned comparisons provided strong evidence of a difference between the treatments. However, up to 6 months, we saw a trend towards a higher rate of all-cause mortality with surgery relative to angioplasty; whereas after 6 months, we recorded a trend towards a

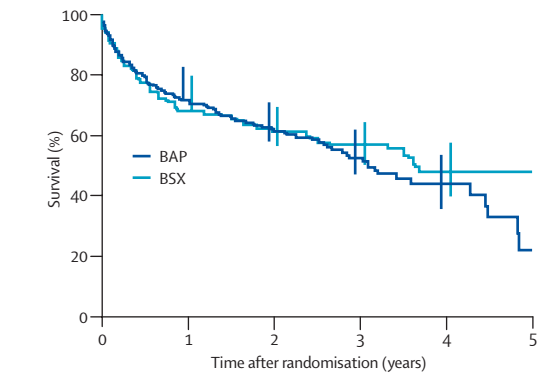

Figure 2: **Amputation-free survival after bypass surgery and balloon angioplasty**
Bars show 95% CIs for survival up to 1, 2, 3, and 4 years of follow-up, which were calculated from the cumulative hazards.

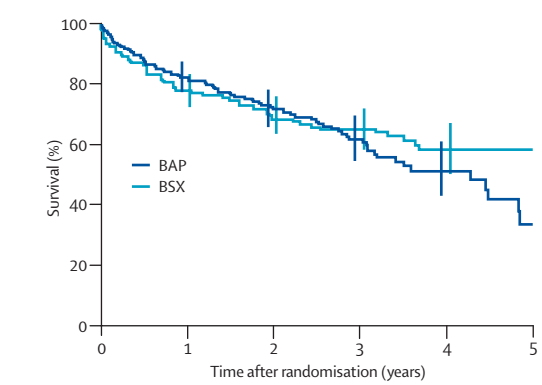

Figure 3: **All-cause mortality after bypass surgery and balloon angioplasty**
Bars show 95% CIs for survival up to 1, 2, 3, and 4 years of follow-up, which were calculated from the cumulative hazards.

reduced hazard in surgery with respect to both all-cause mortality and amputation-free survival.

A post-hoc analysis, done after examination of the survival curves, showed a significantly reduced hazard in amputation-free survival (adjusted HR 0·37 [95% CI 0·17–0·77], p=0·008) and all-cause mortality (0·34 [0·17–0·71], p=0·004) for surgery relative to angioplasty in the period beyond 2 years from randomisation. There was no evidence of differential effectiveness of the interventions from the treatment by covariate interactions for either endpoint, overall or in any of the time periods. The covariates with the strongest independent effect on survival to the endpoints were the clinical stratification group, diabetes, creatinine concentration, and age.

At baseline, the two treatment groups were balanced in terms of HRQL. Patients in both treatment groups reported improved EQ5D and SF36 physical component summary scores by 3 months that were largely sustained during follow-up. However, little further improvement was seen beyond 3 months (table 4). We also recorded improvement over an extended period in the SF36 mental component summary score. Although there is weak evidence suggesting that HRQL may be somewhat better in the surgery group, there are no significant differences in HRQL between the two treatment groups. This finding is consistent across the three HRQL scores.

Table 5 compares the use of hospital resources on an intention-to-treat basis during the first 12 months from randomisation. Inpatient hospital costs per day were estimated at UK£421 for vascular surgical ward days, £591 for high-dependency unit days, and £1526 for intensive-therapy unit days. The average procedure costs were estimated as £3104 for surgery and £1159 for angioplasty.[49] Inpatient costs per day and procedure costs were reported on a price base of the financial year 2003–04. We recorded no difference between the two strategies with respect to the number of hospital admissions. However, patients assigned to receive surgery spent significantly longer in hospital and needed significantly more care in the high-dependency unit and intensive-therapy unit for the first 12 months than did

	Number of events		Hazard ratio (95% CI) of surgery relative to angioplasty	
	Angioplasty (n=224)	Surgery (n=228)	Unadjusted	Adjusted*
Amputation-free survival				
Entire follow-up	106	98	0·89 (0·68–1·17)	0·88 (0·66–1·16)
Up to 6 months	46	50	1·07 (0·72–1·6)	1·04 (0·69–1·56)
After 6 months	60	48	0·75 (0·51–1·1)	0·73 (0·49–1·07)
After 2 years†	28	16	0·44 (0·22–0·88)	0·37 (0·17–0·77)
All-cause mortality				
Entire follow-up	87	79	0·90 (0·66–1·22)	0·95 (0·69–1·29)
Up to 6 months	26	31	1·20 (0·71–2·02)	1·27 (0·75–2·15)
After 6 months	61	48	0·78 (0·53–1·13)	0·81 (0·55–1·19)
After 2 years†	27	11	0·38 (0·19–0·77)	0·34 (0·17–0·71)

*Adjusted for age, sex, clinical stratification group, body-mass index, current or ex-smoker status, creatinine concentration, diabetes, and statin use at baseline. †Post-hoc analysis done after examination of survival curves.

Table 3: **Comparison of hazard of amputation-free survival and all-cause mortality**

	Angioplasty (n=224)	Surgery (n=228)	Crude difference (mean [SE])	Adjusted difference for baseline score (mean [SE], number of patients)	p
EQ5D weighted index score					
Baseline	0·26 (0·32, 215)	0·29 (0·34, 206)	0·03 (0·03)	1	..
0–3 months	0·53 (0·31, 164)	0·57 (0·28, 152)	0·04 (0·03)	0·01 (0·03, 305)	0·87
3–6 months	0·52 (0·34, 144)	0·56 (0·31, 131)	0·05 (0·04)	0·04 (0·04, 267)	0·35
6–12 months	0·55 (0·31, 133)	0·62 (0·29, 119)	0·06 (0·04)	0·05 (0·04, 244)	0·19
SF36 physical component summary					
Baseline	17·50 (7·97, 213)	17·80 (9·06, 207)	0·30 (0·83)	1	..
0–3 months	23·80 (11·88, 163)	24·37 (12·45, 152)	0·57 (1·37)	−0·41 (1·25, 304)	0·74
3–6 months	24·62 (11·58, 144)	24·88 (13·51, 131)	0·26 (1·51)	−0·47 (1·35, 267)	0·73
6–12 months	24·58 (11·70, 133)	26·13 (13·54, 119)	1·56 (1·59)	0·08 (1·57, 245)	0·96
SF36 mental component summary					
Baseline	43·47 (11·64, 213)	45·17 (11·96, 207)	1·69 (1·15)	1	..
0–3 months	47·69 (11·28, 163)	48·68 (11·13, 152)	0·99 (1·26)	0·12 (1·22, 304)	0·92
3–6 months	46·67 (12·19, 144)	48·60 (10·75, 131)	1·93 (1·39)	1·72 (1·38, 267)	0·21
6–12 months	48·26 (11·76, 133)	50·16 (10·60, 119)	1·90 (1·42)	1·67 (1·33, 245)	0·21

Data are mean score (SD, number of patients) unless stated otherwise. Higher scores indicate better HRQL.

Table 4: **Comparison of HRQL by intention-to-treat analysis at different time points from randomisation**

those allocated angioplasty. Thus, 53 (23%) patients given the surgery-first strategy needed high-dependency unit care and nine (4%) needed intensive-therapy unit care during the first 12 months of follow-up compared with one (7%) and 16 (0·5%) patients given the angioplasty-first strategy.

The mean cost of inpatient hospital treatment during the first 12 months of follow-up in patients assigned to a surgery-first strategy was estimated as £23 322 (£20 096 hospital stay, £3225 procedure costs), which is about a third higher than the £17 419 (£15 381, £2039) for patients assigned an angioplasty-first strategy.

	Surgery (n=228)		Angioplasty (n=224)		p*
	Mean (SD)	Range	Mean (SD)	Range	
Number of admissions to hospital	2·14 (1·30)	(1–8)	2·06 (1·50)	(0–10)	0·286
Total days spent in hospital	46·14 (53·87)	(0–365)	36·35 (51·39)	(0–334)	<0·0001
Days spent in intensive therapy unit	0·13 (0·94)	(0–12)	0·04 (0·60)	(0–9)	0·012
Days spent in high dependency unit	0·65 (1·60)	(0–11)	0·18 (1·17)	(0–16)	<0·0001
Number of surgical procedures	0·95 (0·50)	(0–4)	0·26 (0·52)	(0–3)	..
Number of angioplasty procedures	0·25 (0·54)	(0–3)	1·05 (0·36)	(0–3)	..

*Wilcoxon two-sample test.

Table 5: **Comparison of use of hospital resources by intention to treat during first 12 months from randomisation**

Discussion

As a multicentre, randomised controlled trial, BASIL compares the outcome of a bypass-surgery-first strategy with a balloon-angioplasty-first strategy in patients presenting with severe limb ischaemia due to infra-inguinal disease. We found that in the medium term, the outcomes after these two strategies are broadly similar with respect to amputation-free survival, all-cause mortality, and HRQL. However, if the different patient outcomes are analysed in more detail and over different time periods after their first intervention, the relative advantages and disadvantages of each strategy become apparent.

In the short term, a surgery-first strategy was associated with a significantly higher rate of morbidity, significantly greater length of hospital stay, and greater use of the high-dependency unit and intensive-therapy unit than that of an angioplasty-first strategy. Therefore, hospital costs of surgery for the first 12 months after randomisation were about a third higher than those of angioplasty. We recorded a high occurrence of cardiovascular, infective, and wound complications after surgery, and a small but clinically significant re-intervention rate for graft revision, thrombectomy, and evacuation of haematoma. However, the 30-day mortality after surgery, which was not significantly higher than that seen after angioplasty, was low considering the severity of the disease and comorbidity shown by this cohort of patients. The 30-day technical failure rate was also low given the complexity of the surgery.

In the long term, after 2 years, surgery seemed to be associated with a significantly reduced risk of future amputation, death, or both—ie, if a patient was alive with their leg intact at 2 years after randomisation, they seemed to be more likely to remain alive in the future with their leg intact if they had been assigned to receive surgery first than angioplasty first. Although this result is highly significant, we should not overinterpret this finding since it is the result of a post-hoc analysis done after the surgical curves had been viewed, furthermore the numbers of endpoints after 2 years were small. However, this finding raises the intriguing possibility that, despite the increased short-term morbidity, patients could enjoy a more durable benefit from a surgery-first strategy than an angioplasty-first strategy.

We recorded a higher immediate failure and 12-month re-intervention rate in angioplasty than in surgery; however, morbidity associated with angioplasty was low, the hospital stay was short (thus the costs were lower),

and there was no suggestion that a clinically failed angioplasty prejudiced the results of any subsequent surgery intervention that had been deemed necessary and appropriate. Unfortunately, a sizeable minority of patients in both groups underwent repeated procedures only to eventually die or lose their leg (or both) within the first 12 months, which suggests that some patients might have been better served by primary amputation. Not surprisingly, the data indicate that the trial patients had a very low HRQL before treatment. We saw no significant difference in HRQL between the two strategies, which suggests that the patients' overwhelming concern was to have their pain relieved and amputation avoided, and how that was achieved was of much less importance to them in terms of HRQL.[50] There were short-term improvements in perceptions of physical and mental wellbeing but neither treatment led to continuing improvement in HRQL beyond the first few months. This finding could have been because patients with severe limb ischaemia are generally elderly and socially disadvantaged with multiple comorbidities.

The hospital costs over the first year were higher for surgery than for angioplasty. Although the procedural cost of the surgery was greater than that of angioplasty, the main difference was related to the length of hospital stay and, in particular, the much greater need for patients undergoing surgery to be cared for within a high-dependency-unit or intensive-therapy-unit environment. We did not attempt to quantify the use and associated costs of health and social services outside the hospitals. However, this proportion of cost would probably represent a large additional financial burden for certain patients, especially for those who ultimately need amputation.

As stated earlier, there was no evidence base before this trial. Previous studies[6,20–24] comparing the clinical effectiveness and cost-effectiveness of the two strategies for various degrees of lower limb ischaemia have had specific problems[16] such as a lack of controls; small patient numbers; poorly defined patients and interventions; the inclusion, comparison, and combined analysis of patients with intermittent claudication and severe limb ischaemia as well as with aorto-iliac and infra-inguinal disease; retrospective analysis; and short or incomplete follow-up (or both).[18–21,25–32]

Although not the main goal of the trial, it is worth noting that few study patients were on antiplatelet drug treatment and statin therapy and that many patients were current smokers on entry to the trial. The reasons for these characteristics are unclear and probably multifactorial. However, our results have also been seen in other studies of similar groups of patients.[51] Clear evidence shows that so-called best medical therapy (consisting of antiplatelet drugs, smoking cessation, and lipid-lowering therapy) can retard the development and progression of lower limb arterial disease. Best medical therapy is also associated with a large reduction in the risk of future cardiovascular events, including the need for limb-salvage intervention and amputation.[3] How many of the BASIL trial patients, had they been receiving best medical treatment, would have avoided severe limb ischaemia and its consequences? An aggressive implementation of best medical treatment might have also improved the results of the trial interventions. Improvement of the medical management of patients with and at risk of developing severe limb ischaemia would seem to be an urgent priority in primary and secondary care.

The BASIL trial clearly indicates that, almost irrespective of what treatment is received, many patients with severe limb ischaemia have an extremely poor prognosis. Furthermore, our audit shows that up to half the patients presenting with severe limb ischaemia to major UK vascular units and undergoing diagnostic imaging are regarded as unsuitable or unfit for any form of revascularisation. Furthermore, an additional group of patients with severe limb ischaemia are not offered diagnostic imaging because their disease is too advanced or their medical condition is too poor. Thus, patients who undergo revascularisation for severe limb ischaemia, either by surgery or angioplasty, seem to represent the tip of an iceberg, the true dimensions of which remain incompletely defined. This result means that any randomised trial of interventions for severe limb ischaemia, including BASIL, will be restricted in its generalisability to the entire population of patients with the disorder, many of whom are actually treated conservatively or by primary amputation. However, the BASIL audit indicated that about a third of patients with severe limb ischaemia who undergo diagnostic imaging and are regarded as suitable for revascularisation, fell into the trial's grey area of equipoise; and more than two-thirds of these were randomised. Thus, the results of the BASIL trial are applicable and generalisable to very large numbers of patients presenting to vascular units with severe limb ischaemia and undergoing attempted revascularisation worldwide.

In summary, severe limb ischaemia imposes a very high human cost as well as a major economic burden on health and social care, not only in developed countries, but also increasingly in developing countries. We hope that the BASIL trial data will help vascular surgeons and radiologists advise, and obtain fully informed consent from, their patients in the knowledge that the decision-making process is based on level 1 evidence regarding the relative risks and benefits of strategies of bypass surgery first and balloon angioplasty first. The medium-term results of the BASIL trial indicate that patients presenting with severe limb ischaemia due to infra-inguinal atherosclerosis and who seem technically suitable for both treatments can reasonably be treated with either method in the first instance, depending on individual characteristics and local expertise. However, notwithstanding the high failure and re-intervention rate

associated with angioplasty, patients who are expected to live for less than 1–2 years and have significant comorbidity should probably, when possible, be offered angioplasty first. Thus, even if the procedure fails, the patient may not be disadvantaged in the short term and can go on to have surgery if regarded as appropriate. Angioplasty also seems to be a much less expensive option than surgery, at least in the short term. By contrast, in patients expected to live more than 2 years and who are relatively fit, the apparent improved durability and reduced re-intervention rate of surgery could outweigh the short-term considerations of increased morbidity and cost. Long-term follow-up and a detailed analysis of the BASIL trial dataset will probably allow these provisional recommendations to be refined in the future.

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Contributions of the writing committee—D J Adam, J D Beard, and T Cleveland participated in data analysis and writing of the paper. J Bell was the BASIL trial coordinator and participated in trial management, data collection, data analysis, and writing of the paper. A W Bradbury, was the principal investigator and participated in all aspects of trial design, grant application, delivery, analysis of the trial, and writing of the paper. J F Forbes was a grant co-applicant; participated in the trial design, data analysis, and writing of the paper; and had special responsibility for HRQL and health economics. F G R Fowkes, I Gillepsie, and C V Ruckley were grant co-applicants and participated in the trial design, data analysis, and writing of the paper. G Raab was the trial statistician; and participated in design of the statistical plan, performance of the statistical analysis, and writing of the paper with special responsibility of the statistical sections and presentation of data. H Storkey participated in the performance of the statistical analysis and writing of the paper.

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Conflict of interest statement

The members of the writing committee declare that they have no conflict of interest.

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