A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial

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Summary

Background Chronic limb-threatening ischaemia is the severest manifestation of peripheral arterial disease and presents with ischaemic pain at rest or tissue loss (ulceration, gangrene, or both), or both. We compared the effectiveness of a vein bypass first with a best endovascular treatment first revascularisation strategy in terms of preventing major amputation and death in patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularisation procedure to restore limb perfusion.

Methods Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL)-2 was an open-label, pragmatic, multicentre, phase 3, randomised trial done at 41 vascular surgery units in the UK (n=39), Sweden (n=1), and Denmark (n=1). Eligible patients were those who presented to hospital-based vascular surgery units with chronic limb-threatening ischaemia due to atherosclerotic disease and who required an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularisation procedure to restore limb perfusion. Participants were randomly assigned (1:1) to receive either vein bypass (vein bypass group) or best endovascular treatment (best endovascular treatment group) as their first revascularisation procedure through a secure online randomisation system. Participants were excluded if they had ischaemic pain or tissue loss considered not to be primarily due to atherosclerotic peripheral artery disease. Most vein bypasses used the great saphenous vein and originated from the common or superficial femoral arteries. Most endovascular interventions comprised plain balloon angioplasty with selective use of plain or drug eluting stents. Participants were followed up for a minimum of 2 years. Data were collected locally at participating centres. In England, Wales, and Sweden, centralised databases were used to collect information on amputations and deaths. Data were analysed centrally at the Birmingham Clinical Trials Unit. The primary outcome was amputation-free survival defined as time to first major (above the ankle) amputation or death from any cause measured in the intention-to-treat population. Safety was assessed by monitoring serious adverse events up to 30-days after first revascularisation. The trial is registered with the ISRCTN registry, ISRCTN27728689.

Findings Between July 22, 2014, and Nov 30, 2020, 345 participants (65 [19%] women and 280 [81%] men; median age 72·5 years [62·7–79·3]) with chronic limb-threatening ischaemia were enrolled in the trial and randomly assigned: 172 (50%) to the vein bypass group and 173 (50%) to the best endovascular treatment group. Major amputation or death occurred in 108 (63%) of 172 patients in the vein bypass group and 92 (53%) of 173 patients in the best endovascular treatment group (adjusted hazard ratio [HR] 1·35 [95% CI 1·02–1·80]; p=0·037). 91 (53%) of 172 patients in the vein bypass group and 77 (45%) of 173 patients in the best endovascular treatment group died (adjusted HR 1·37 [95% CI 1·00–1·87]). In both groups the most common causes of morbidity and death, including that occurring within 30 days of their first revascularisation, were cardiovascular (61 deaths in the vein bypass group and 49 in the best endovascular treatment group) and respiratory events (25 deaths in the vein bypass group and 23 in the best endovascular treatment group; number of cardiovascular and respiratory deaths were not mutually exclusive).

Interpretation In the BASIL-2 trial, a best endovascular treatment first revascularisation strategy was associated with a better amputation-free survival, which was largely driven by fewer deaths in the best endovascular treatment group. These data suggest that more patients with chronic limb-threatening ischaemia who required an infra-popliteal, with

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or without an additional more proximal infra-inguinal, revascularisation procedure to restore limb perfusion should be considered for a best endovascular treatment first revascularisation strategy.

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Introduction

Chronic limb-threatening ischaemia, previously known as critical limb ischaemia and severe ischaemia of the leg, is the most severe form of peripheral arterial disease due to atherosclerosis and presents with ischaemic rest pain (usually worse at night) and tissue loss (ulceration, gangrene, or both) usually affecting the foot, or both.[1–3] Mainly because of tobacco smoking and the growing prevalence of type 2 diabetes, chronic limb-threatening ischaemia represents a growing burden on health and social care services across the world.[4,5] Unless the blood supply to the affected limb is restored, patients with chronic limb-threatening ischaemia are at high risk of amputation or death. Although it is universally agreed that—in addition to best medical therapy—virtually all patients with chronic limb-threatening ischaemia should at least be considered for revascularisation, there is continuing debate as to whether such revascularisation is best achieved by inserting a bypass graft—preferably using a vein taken from the patient's own leg (vein bypass)—or through best endovascular treatment, which in most cases will be balloon angioplasty with or without the use of stents.[6] The scarcity of high quality evidence, especially regarding infra-popliteal revascularisation,[7] is readily apparent in the published literature, and is also reflected in the low strength of recommendations found within various international guidelines.[8–11] Even after initially successful revascularisation, patients with chronic limb-threatening ischaemia often require multiple procedures to maintain limb perfusion and frequent hospital readmissions for limb-related problems and other comorbidities, most commonly ischaemic heart and respiratory disease, which usually coexist in this patient population. As a result, chronic limb-threatening ischaemia is associated with high resource use and poor health-related quality of life (HRQoL).[12,13] The UK Bypass versus Angioplasty in Severe Ischaemia of the Leg Trial (BASIL-1) trial, which included 452 participants, suggested that patients with chronic limb-threatening ischaemia anticipated to have a life expectancy of 2 years or more and who had a suitable vein for bypass, should be offered vein bypass first in preference to balloon angioplasty.[14–17] The Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischaemia (BEST-CLI) trial[18] included 1830 participants, mainly from the USA. In a cohort of 1434 patients who had an optimal (single segment great saphenous) vein for bypass, the incidence of a composite endpoint comprising major adverse limb events or death from any cause was significantly lower in the vein bypass group than in the best endovascular treatment group. In a second cohort of 396 participants who did not have optimal single segment great saphenous vein for bypass, outcomes were similar between treatment groups.[18]

The severity and anatomical distribution of atherosclerosis affects treatment options and outcomes in chronic limb-threatening ischaemia.[19,20] About three quarters of participants in the BASIL-1 trial had a vein or prosthetic bypass, or a plain balloon angioplasty, for disease in the femoro-popliteal segment: the arteries between the hip and the knee. A subsequent subgroup analysis of participants in the BASIL-1 trial[21] who

Research in context

Evidence before this study

In 2012, the UK National Institute for Health and Care Excellence established that no randomised trial had specifically compared a vein bypass first with a best endovascular treatment first revascularisation strategy in patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularisation procedure to restore limb perfusion. A recent systematic review has confirmed this to still be the case.

Added value of this study

BASIL-2 is the only randomised trial to specifically compare a vein bypass first with best endovascular treatment first revascularisation strategy in patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularisation procedure to restore limb perfusion. Our findings suggest that a best endovascular treatment first revascularisation strategy is associated with a better amputation-free survival. This is mainly because the best endovascular treatment first revascularisation strategy resulted in fewer deaths. Limb-related outcomes were similar between groups.

Implications of all the available evidence

These data suggest that more patients with chronic limb threatening ischaemia who require an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularisation procedure to restore limb perfusion should be considered for a best endovascular treatment first revascularisation strategy.

underwent infra-popliteal revascularisation also suggested that outcomes might be better with vein bypass than plain balloon angioplasty, but this finding was associated with a high level of uncertainty.

Mainly because of the growing importance of type 2 diabetes as a major worldwide risk factor for chronic limb-threatening ischaemia, but also due to the increased numbers of patients with end-stage renal disease, a growing proportion of patients with chronic limb-threatening ischaemia have, often heavily calcified, infra-popliteal disease requiring treatment. Establishing an evidence base for different revascularisation strategies in this specific patient group is increasingly important. In 2012, the UK National Institute for Clinical and Health Excellence recommended that a randomised trial be done to compare a vein bypass first with a best endovascular treatment first revascularisation strategy specifically in patients with chronic limb-threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularisation procedure to restore limb perfusion.[1] The aim of BASIL-2 was to specifically determine whether, in such patients, a vein bypass first or a best endovascular treatment first revascularisation strategy was associated with a better clinical outcome in terms of major (above the ankle) amputation or death from any cause (amputation-free survival). BASIL-2 also included a health economic analysis, which will be reported separately.

Methods

Study design and participants

BASIL-2 was an open-label, pragmatic, multicentre, phase 3 trial done in 41 vascular surgery units in the UK (n=39), Sweden (n=1), and Denmark (n=1). Eligible participants were patients who presented to hospital-based vascular surgery units with chronic limb-threatening ischaemia due to atherosclerotic disease and who required an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularisation procedure to restore limb perfusion. Inclusion criteria included life expectancy of more than 6 months, and judged by a minimum of two consultants (at least one of whom could undertake infra-popliteal vein bypass and one of whom could undertake infra-popliteal endovascular interventions in their clinical practice) to require and be suitable for both infra-popliteal vein bypass and infra-popliteal endovascular intervention. Eligible patients were not permitted to have had previous vascular intervention to the target infra-popliteal artery within the previous 12 months, but did need to have adequate aortoiliac inflow to support both revascularisation strategies. Patients had to be able and willing to complete HRQoL and health economic questionnaires (with help if required) and be able to understand sufficient English, Swedish, or Danish (depending on country of recruitment) to ensure informed consent. Participants were excluded if they had ischaemic pain or tissue loss considered not to be primarily due to atherosclerotic peripheral artery disease.

All participants provided written informed consent. Ethics approval was obtained from the National Research Ethics Service, based in the West Midlands, Coventry, UK (14/WM/0057). The trial was done in accordance with the declaration of Helsinki and Good Clinical Practice guidelines. The protocol has been published.[22]

Randomisation and masking

Participants were randomly assigned (1:1) to receive either vein bypass (vein bypass group) or best endovascular treatment (best endovascular treatment group) as their first revascularisation procedure through a secure online randomisation system. Minimisation was used to balance trial-group assignments according to age (≤60 years, 61–70 years, 71–80 years, or >80 years); gender (men *vs* women); type 2 diabetes only, chronic kidney disease only, both, or neither; severity of clinical disease (ischaemic rest or night pain only, tissue loss only, or both); previous (permissible) intervention to the trial leg (yes *vs* no); and intention for a hybrid procedure (yes *vs* no). Country of recruitment (UK, Sweden, or Denmark) was not included as a minimisation variable because BASIL-2 was initially planned to be completed entirely within the UK. The randomisation system was provided centrally by the Birmingham Clinical Trials Unit, University of Birmingham, Birmingham, UK. BASIL-2 was an open-label study; participants, study staff, and investigators were not masked to treatment allocation.

Procedures

The pragmatic trial design encouraged vascular and endovascular surgeons and interventional radiologists to perform vein bypass and best endovascular treatment using their preferred equipment, devices, and surgical and anaesthetic techniques. For vein bypass, any vein deemed suitable by the responsible vascular surgeons could be used. If at operation it was discovered that the vein could not be used, then composite or prosthetic grafts could be inserted at the surgeon's discretion in the patient's best interests. Regarding best endovascular treatment, any device being used as part of standard of care in that country was permissible. Drug coated balloons, bare metal stents, and drug eluting stents could be used at the operator's discretion. Atherectomy devices were permitted but not used. In this pragmatic trial, all additional management strategies, including additional procedures, were at the responsible clinicians' discretion in the patient's best interests.

Patients were followed up locally at 1 month after the first revascularisation procedure; 6, 12, and 24 months after randomisation; and then annually until the last recruited participant had been followed up for 24 months. HRQoL and clinical data were collected at

each visit when possible, including amputation and death data. However, from March, 2020, onwards, components of data collection that required a face-to-face assessment, such as haemodynamic measurements, were substantially affected by the COVID-19 pandemic. In England and Wales, the primary outcome data were also obtained until the end of follow-up from NHS Digital (NHS Digital is the statutory custodian for health and social care data for England and Wales). In the Swedish centre, the Regional Electronic Health Data system was also used to check for amputations, hospitalisations, or deaths. In the Danish centre all data were collected locally; electronic health data systems were not used.

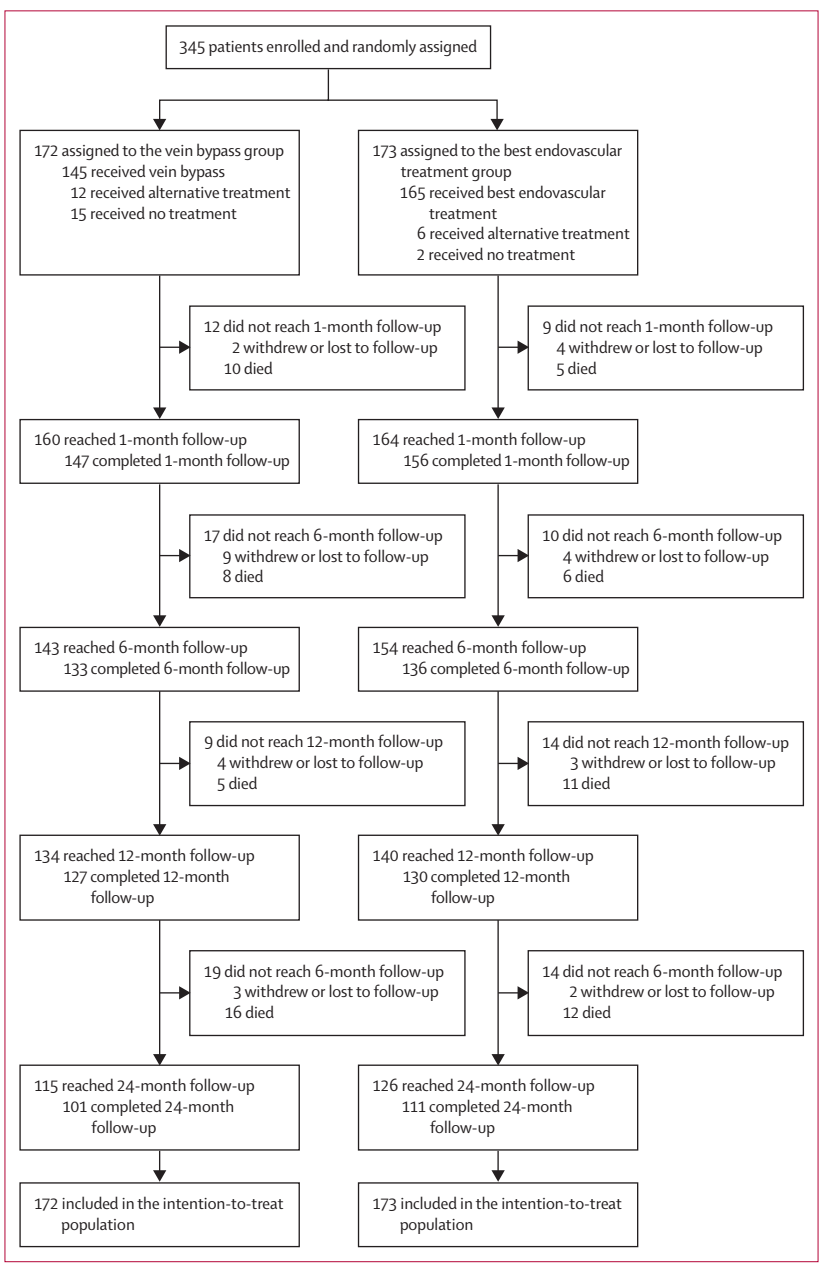

Figure 1: **Trial profile**

Outcomes

The primary outcome was amputation-free survival defined as time to major (above the ankle) amputation of the trial leg or death from any cause (whichever occurred first).

Time to event secondary outcomes were time to death from any cause (overall survival), time to major amputation of the trial leg, time to first major adverse limb event (MALE; defined as major amputation of the trial leg or any additional major revascularisation intervention to the trial leg, following the first revascularisation intervention), and time to first major adverse cardiac event (MACE; defined as chronic limb-threatening ischaemia or major amputation affecting the non-trial leg, myocardial infarction, transient ischaemic attack, or stroke). Binary secondary outcomes measured at a single time point were any MALE, any MACE, additional major revascularisation intervention to the trial leg (following the first revascularisation intervention), reintervention (defined as a repeat of the same type of procedure [eg, vein bypass followed by an additional bypass]), crossover intervention (defined as an alternative revascularisation procedure to the first procedure after randomisation [eg, vein bypass followed by an endovascular procedure]), and morbidity and death within 30 days of the first revascularisation. Binary secondary outcomes measured at multiple time points were healing of tissue loss (ulceration, gangrene, or both) at or below the ankle presumed to be caused by atherosclerotic peripheral artery disease as assessed by the Wound Ischaemia and foot Infection tool and relief of ischaemic pain as determined by opiate usage. Continuous secondary outcomes were relief of ischaemic pain as determined by visual analogue scale; HRQoL using generic (Euroqol 5L [EQ-5D-5L], Short Form-12 [SF-12], and ICEpop CAPability measure for Older people [ICECAP-O]) and disease specific (the Vascular Quality of Life Questionnaire [VascuQoL]) tools; healing of tissue loss assessed by the perfusion, extent, depth, infection, and sensation (PEDIS) score; and haemodynamic measurements comprising ankle brachial pressure index (ABPI) and toe brachial pressure index (TBPI).[23,24]

Safety was assessed by monitoring serious adverse events up to 30-days after first revascularisation. We predefined adherence as participants who received their allocated intervention as their first revascularisation after randomisation. Subsequent interventions were not considered part of the adherence definition because they were captured as secondary outcomes.

Statistical analysis

The original sample size was based on a time-to-event analysis to be undertaken 2 years after completion of

recruitment. It was anticipated that recruitment would take place over 3 years: 20% of patients recruited in year 1, 40% in year 2, and 40% in year 3. On the basis of the BASIL-1 trial,[14] amputation-free survival rates were assumed to be 0·72 in year 1, 0·62 in year 2, 0·53 in year 3, 0·47 in year 4, and 0·35 in year 5. Allowing for a 10% attrition rate and based on the survival estimates calculated using the BASIL-1 data, a population of 600 participants (247 primary outcome events) would have 90% power to detect a reduction in amputation-free survival of one-third (hazard ratio [HR] 0·66) at the 5% significance level using the artsurv (version 1.0.7) programme in Stata (version 17.0). We used a superiority framework because vein bypass is a more invasive procedure and potentially associated with greater resource use.

The initial assumptions made in this trial concerning recruitment rates were not achieved; therefore, recruitment continued beyond year 3. As a result, the median length of follow-up was longer than originally planned. Therefore, the number of randomly assigned patients required to observe 247 events (as per the original sample size target) was reduced due to the increased exposure time. With support of the funder and independent oversight from the Data Monitoring Committee, recruitment rates, length of follow-up, and pooled event rates over time were modelled to predict the number of participants needed to reach 247 events, with 24 months minimum follow-up in each patient. The modelling was updated approximately every 6 months based on emerging data. Due to ongoing challenges with recruitment, largely related to the COVID-19 pandemic, the BASIL-2 trial closed to recruitment on Nov, 30 2020, with 345 participants randomly assigned.

A comprehensive statistical analysis plan was specified before analysis. The primary, secondary, and safety outcomes were analysed in the intention-to-treat population (all randomly assigned participants irrespective of adherence with the treatment protocol). All estimates of differences between groups were presented with two-sided 95% CIs, adjusted for the minimisation variables as fixed effects (when convergence was possible) and recruiting centre as a random effect (or as a shared frailty variable in time-to-event analyses). EQ-5D-5L, SF-12, ICECAP-O, VascuQoL, ABPI, TBPI, PEDIS, and visual analogue scale were also adjusted for baseline value.

The primary outcome was analysed using a Cox proportional hazards model to generate an HR adjusted for the minimisation factors and recruitment site. Statistical significance of the treatment group parameter was determined through examination of the associated χ^2 statistic. Kaplan-Meier survival curves were constructed for visual presentation of time-to-event comparisons.

Time-to-event secondary outcomes were analysed as per the primary outcome, but they were not subjected to hypothesis testing. For time-to-event secondary outcomes,

	Vein bypass group (n=172)	Best endovascular treatment group (n=173)
Sex*		
Female	33 (19%)	32 (18%)
Male	139 (81%)	141 (82%)
Median age, years	72·4 (64·3–78·7)	72·5 (62·7–79·7)
Age groups (years)*		
≤60	38 (22%)	36 (21%)
61–70	42 (24%)	44 (25%)
71–80	61 (35%)	58 (34%)
>80	31 (18%)	35 (20%)
Race		
White	157 (91%)	158 (91%)
Black	8 (5%)	9 (5%)
Asian	5 (3%)	5 (3%)
Other†	1 (1%)	0
Declined to provide or missing	1 (1%)	1 (1%)
Country of recruitment		
UK	147 (85%)	146 (84%)
Sweden	18 (11%)	18 (10%)
Denmark	7 (4%)	9 (5%)
Diabetes		
Patients with diabetes*	117 (68%)	120 (69%)
Patients with insulin dependent diabetes	62/117 (53%)	61/120 (51%)
No data	0	1/120 (1%)
Patients with chronic kidney disease*‡	58 (34%)	60 (35%)
Severity of clinical disease on the trial leg*		
Rest or night pain only	22 (13%)	19 (11%)
Tissue loss only	39 (23%)	32 (18%)
Both	111 (64%)	122 (71%)
Trial leg interventions		
Previous (permissible) intervention to the trial leg*§	20 (12%)	22 (13%)
Unknown	77 (45%)	76 (44%)
Hybrid procedure planned*§	4 (2%)	4 (2%)
Unknown	77 (45%)	76 (44%)
Leg enrolled in the trial		
Right	74 (43%)	95 (55%)
Left	98 (57%)	78 (45%)
BMI		
Data available	149 (87%)	154 (89%)
No data	23 (13%)	19 (11%)
BMI (kg/m^2)	27·1 (4·9)	26·8 (5·5)
Estimate glomerular filtration rate (mL/min per 1·73 m^2)	66·5 (23·2)	67·6 (24·3)
Living arrangement		
Own Home	135 (78%)	142 (82%)
Other Acute Hospital	1 (1%)	1 (1%)
Residential Home	0	1 (1%)
Nursing Home	0	1 (1%)
Other	8 (5%)	6 (4%)
No data	28 (16%)	22 (13%)

(Table 1 continues on next page)

	Vein bypass group (n=172)	Best endovascular treatment group (n=173)
(Continued from previous page)		
Mobility		
Fully ambulant without walking aid	84 (49%)	69 (40%)
Ambulant with walking aid	73 (42%)	93 (54%)
Wheelchair bound	13 (8%)	10 (6%)
Bed-bound	1 (1%)	1 (1%)
No data	1 (1%)	0
Smoking status		
Never	58 (34%)	48 (28%)
Ex-smoker	75 (44%)	92 (53%)
Current	38 (22%)	33 (19%)
No data	1 (1%)	0
Medical history		
Previous stroke	25 (15%)	34 (20%)
Missing	1 (1%)	0
Previous myocardial infarction	41 (24%)	23 (13%)
Missing	1 (1%)	0
Previous angina	22 (13%)	21 (12%)
Missing	1 (1%)	1 (1%)
Previous CABG	22 (13%)	15 (9%)
Missing	1 (1%)	0
Previous PCI	23 (13%)	17 (10%)
Missing	1 (1%)	2 (1%)
Previous dialysis	10 (6%)	5 (3%)
Missing	1 (1%)	0
Any previous vascular intervention to the trial leg	54 (31%)	67 (39%)
Missing	1 (1%)	0
Any previous vascular intervention to the non-trial leg	39 (23%)	58 (34%)
Missing	1 (1%)	0
Any antiplatelet use¶	131 (76%)	138 (80%)
Missing	3 (2%)	1 (1%)
Treatment for hypercholesterolaemia-	129 (75%)	138 (80%)
Missing	3 (2%)	2 (1%)
Treatment for hypertension	128 (74%)	129 (75%)
Missing	4 (2%)	1 (1%)
Any anticoagulant use‖	46 (27%)	50 (29%)
Missing	3 (2%)	2 (1%)
Used opiates	89 (52%)	81 (47%)
Missing	3 (2%)	1 (1%)
Imaging method		
Duplex ultrasound	39 (23%)	37 (21%)
MRA	34 (20%)	43 (25%)
CT angiography	44 (26%)	45 (26%)
DSA	50 (29%)	44 (25%)
Missing	5 (3%)	4 (2%)

Data are n (%), n/N (%), mean (SD), or median (IQR). CABG=coronary artery bypass graft. DSA=digital subtraction angiography. MRA=magnetic resonance angiograph, PCI=percutaneous coronary intervention. *Minimisation variable. †Patient was Lebanese. ‡Chronic kidney disease defined as stage 3 or worse based on estimated glomerular filtration rate of less than 60 mL/min per 1·73 m². §Previous (permissible) intervention to the trial leg and intention for a hybrid procedure were both added to the randomisation algorithm partway through recruitment to BASIL-2. ¶Aspirin, clopidogrel, or other antiplatelet use. ‖Warfarin or other anticoagulant use.

Table 1: **Baseline characteristics**

post-hoc sensitivity analyses were considered in a competing risk framework to account for patients who had died before having an event. For continuous secondary outcome measures, adjusted mean differences were estimated at the primary timepoints (1, 12, and 24 months) using mixed effect repeated measures models.[25] Binary secondary outcomes measured at a single timepoint were analysed using a mixed effects log-binomial model to generate an adjusted risk ratio (RR) and risk difference (with an identity link function). Binary secondary outcomes measured at multiple assessment times were analysed using a mixed effects repeated measures logistic regression model to generate adjusted odds ratios at the primary timepoints (1, 12, and 24 months).

Sensitivity and supportive analyses of the primary outcome included a per-protocol analysis, which included only patients regarded as adherent, and an as-treated analysis, in which participants were analysed according to what they received for their first revascularisation intervention. Additional analyses of the primary outcome included assessment of the proportional hazards assumption, assessed graphically and by fitting time-dependent effects.

Pre-planned subgroup analyses of the primary outcome were completed for the minimisation variables in addition to baseline ABPI (<0·8, 0·8–1·2, >1·2, or non-compressible) and baseline TBPI (<0·6, ≥0·6, or non-compressible). The effects of these subgroups were examined by adding the subgroup by treatment group interaction parameters to the regression model. p values from the tests for statistical heterogeneity were presented alongside the effect estimate and estimates of uncertainty within each subgroup. In addition, ratios of HRs were provided to quantify the difference between the treatment effects estimated within each subgroup.

All analyses were done in SAS (version 9.4) or Stata (version 17.0). A Trial Steering Committee provided independent oversight of the trial. Interim analyses of effectiveness and safety endpoints were done on behalf of the Data Monitoring Committee on an approximately annual basis during recruitment; no reason to recommend halting the trial was identified. These analyses were done with the use of the Haybittle–Peto principle and hence no adjustment was made to the final p value.[26] The trial is registered with the ISRCTN registry, ISRCTN27728689.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the results for publication.

Results

Between July 22, 2014, and Nov 30, 2020, 345 patients (65 [19%] women and 280 [81%] men; median age 72·5 years [IQR 62·7–79·3]) with chronic limb-threatening ischaemia were randomly assigned: 172 (50%) to the vein bypass group and 173 (50%) to the

best endovascular treatment group (figure 1). At the end of follow-up (median 40·0 months [IQR 20·9–60·6]) on Nov 30, 2022, 200 primary outcome events had been observed. All patients were included in the primary analysis of amputation-free survival. Baseline characteristics at enrolment are reported in table 1. Adherence to allocated intervention was high: 145 (84%) patients in the vein bypass group and 165 (95%) in the best endovascular treatment group. 309 (94%) of 328 patients received their first revascularisation intervention within 4 weeks of randomisation (appendix p 1). Interventional radiologists performed 147 (84%) of 175 best endovascular treatment first revascularisations.

108 (63%) of 172 patients in the vein bypass group and 92 (53%) of 173 patients in the best endovascular treatment group had a major amputation or died (adjusted HR 1·35 [95% CI 1·02–1·80]; p=0·037; table 2; figure 2). The median amputation-free survival was 3·3 years [IQR 2·1–4·3] in the vein bypass group and 4·4

See Online for appendix

	Vein bypass group (n=172)	Best endovascular treatment group (n=173)	Estimate (95% CI)
Primary outcome			
No amputation-free survival	108 (63%)	92 (53%)	HR 1·35* (1·02 to 1·80); p=0·037
Secondary outcomes			
Death from any cause	91 (53%)	77 (45%)	HR 1·37* (1·00 to 1·87)
Major amputation	35 (20%)	32 (18%)	HR 1·23* (0·75 to 2·01)
30-day morbidity	79 (46%)	73 (42%)	RR 1·11† (0·89 to 1·39); RD 0·06‡ (–0·04 to 0·16)
30-day mortality	10 (6%)	5 (3%)	RR 2·45† (0·84 to 7·20); uRD 0·03§ (–0·01 to 0·07)
MALE	71 (41%)	77 (45%)	HR 0·93* (0·67 to 1·29); RR 0·94† (0·73 to 1·20); RD –0·04‡ (–0·15 to 0·06)
MACE	68 (40%)	73 (42%)	HR 1·09* (0·78 to 1·53); RR 0·95† (0·79 to 1·15); uRD –0·03§ (–0·13 to 0·08)
Opiate use			
1 month	58/146 (40%)	58/151 (38%)	OR 1·10¶ (0·51 to 2·41)
12 months	33/124 (27%)	31/128 (24%)	OR 1·39¶ (0·57 to 3·42)
24 months	21/99 (21%)	32/111 (29%)	OR 0·53¶ (0·20 to 1·43)
Subsequent intervention	50 (29%)	56 (32%)	RR 0·94† (0·68 to 1·28); uRD –0·03§ (–0·13 to 0·06)
Reintervention	9 (5%)	33 (19%)	RR 0·27† (0·13 to 0·55); uRD -0·14§ (–0·21 to –0·07)
Crossover intervention	46 (27%)	33 (19%)	RR 1·43† (0·94 to 2·18); uRD 0·08§ (–0·01 to 0·17)
PEDIS‖			
1 month	6·1 (1·8; 66 patients)	7·1 (2·0; 90 patients)	MD –0·66** (–1·27 to –0·06)
12 months	5·7 (2·5; 19 patients)	5·8 (2·1; 23 patients)	MD –0·05** (–1·21 to 1·11)
24 months	6·5 (0·7; 2 patients)	5·4 (1·3; 17 patients)	MD 0·03** (–2·57 to 2·62)
WIfI††			
1 month	17/51 (33%)	30/66 (45%)	OR 0·49¶ (0·18 to 1·31)
12 months	5/12 (42%)	2/11 (18%)	OR 4·18¶ (0·45 to 39·02)
24 months	1/3 (33%)	4/10 (40%)	OR 1·64¶ (0·06 to 47·28)
ABPI			
1 month	1·0 (0·3; 60 patients)	0·9 (0·3; 67 patients)	MD 1·28‡‡ (–0·01 to 0·26)
12 months	0·9 (0·4; 38 patients)	0·8 (0·3; 36 patients)	MD 0·08‡‡ (–0·09 to 0·25)
24 months	1·0 (0·3; 23 patients)	0·8 (0·3; 26 patients)	MD 0·08‡‡ (–0·13 to 0·28)
TBPI			
1 month	0·4 (0·4; 22 patients)	0·3 (0·3; 25 patients)	MD 0·08‡‡ (–1·0 to 0·26)
12 months	0·5 (0·4; 12 patients)	0·4 (0·5; 9 patients)	MD –0·01‡‡ (–0·28 to 0·25)
24 months	0·7 (0·4; 7 patients)	0·3 (0·3; 10 patients)	MD 0·22‡‡ (–0·05 to 0·49)

Data are n (%), n/N (%), or mean (SD; n), unless otherwise stated. ABPI=ankle to brachial pressure index. HR=hazard ratio. MACE=major adverse cardiac event. MD=mean difference. MALE=major adverse limb event. OR=odds ratio. RD=risk difference. RR=risk ratio. TBPI=toe to brachial pressure index. uRD=unadjusted risk difference. WIFi=wound, ischemia, and foot infection. *Adjusted for the minimisation variables and centre; values less than one favoured the vein bypass group. †Adjusted for the minimisation variables and centre; values less than one favoured the vein bypass group. ‡Adjusted for the minimisation variables and centre; values less than zero favoured the vein bypass group. §Covariates removed from the model due to convergence issues; values less than zero favoured the vein bypass group. ¶Adjusted for the minimisation variables and centre; values less than one favoured the vein bypass group. ‖In participants who reported tissues loss at or below the ankle at that timepoint. **MD adjusted for the minimisation variables and centre and baseline score; values less than zero favoured the vein bypass group. ††In participants who reported tissue loss at or below the ankle at that timepoint; those considered to have moderate or high risk of amputation. ‡‡Adjusted for the minimisation variables, centre and baseline score; values more than zero favoured the vein bypass group.

Table 2: **Primary and secondary clinical outcomes**

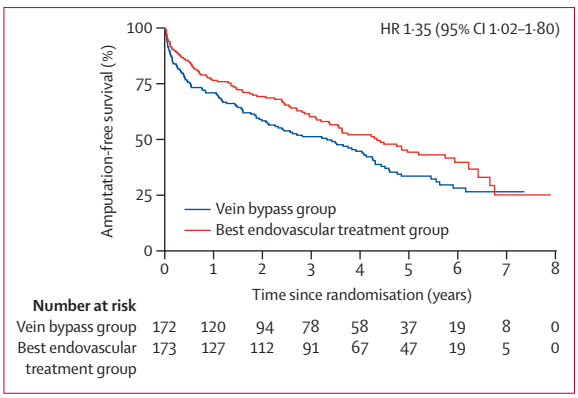

Figure 2: **Amputation-free survival Kaplan-Meier curve**
HR=hazard ratio.

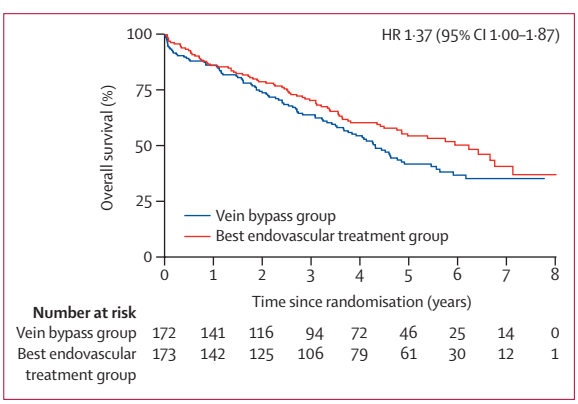

Figure 3: **Overall survival Kaplan-Meier curve**
HR=hazard ratio.

years [IQR 3·4–5·9] in the best endovascular group. Sensitivity analyses supported increased risk of major amputation or death in the vein bypass group (appendix p 4). There was no evidence of varying effects in the prespecified subgroup analyses (appendix p 11). No evidence of non-proportional hazards was observed.

91 (53%) of 172 patients in the vein bypass group and 77 (45%) of 173 in the best endovascular treatment group died from any cause (adjusted HR for overall survival 1·37 [95% CI 1·00–1·87; figure 3). 35 (20%) of 172 in the vein bypass group and 32 (18%) of 173 patients in the best endovascular treatment group had a major amputation (adjusted HR 1·23 [95% CI 0·75–2·01]).

There was no difference in the number of participants who had at least one revascularisation procedure in the trial leg following their first revascularisation intervention between the vein bypass group (50 [29%] of 172 patients) and best endovascular treatment group (56 [32%] of 173; adjusted RR 0·94 [95% CI 0·68–1·28]). However, the number of patients who had a reintervention was higher in the best endovascular treatment group (33 [19%] patients) than in the vein bypass group (nine [5%] patients; 0·27 [0·13–0·55]). Conversely, crossover interventions were more common in the vein bypass group (46 [27%] patients) than in the best endovascular treatment group (33 [19%] patients; 1·43 [0·94–2·18]). There were no differences between the two treatment groups in 30-day morbidity and death, MALE, MACE, relief of ischaemic pain, or HRQoL (tables 2, 3). 29 (17%) patients in the vein bypass group and 23 (13%) patients in the best endovascular treatment group had a serious adverse event (appendix pp 12–14). In the best endovascular treatment group, one serious adverse event (biliary sepsis due to gallstones complicated by pancreatitis and organ failure) was considered related to trial intervention and was unexpected. In most cases, cause of death was reported as multifactorial and often related to multiple comorbidities (appendix pp 5–10). Cardiovascular (61 deaths in the vein bypass group and 49 in the best endovascular treatment group) and respiratory events (25 deaths in the vein bypass group and 23 in the best endovascular treatment group; number of cardiovascular and respiratory deaths were not mutually exclusive) were the most common causes of death in both groups. There were no specific causes of death identified in either trial group which would explain the differences in number of deaths observed between the two groups. The results from the post-hoc sensitivity analyses for time-to-event secondary outcomes are reported in the appendix (p 4).

Discussion

The BASIL-2 trial shows that, in patients with chronic limb-threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularisation procedure to restore limb perfusion, a vein bypass first revascularisation strategy was associated with an increased risk of major amputation or death from any cause compared with a best endovascular treatment first revascularisation strategy. The difference in amputation-free survival was mainly driven by fewer deaths in the best endovascular treatment first group; limb-based outcomes were similar between the groups. The 30-day post-procedural morbidity and death rates were not significantly different between the two groups, and the causes of death in the two groups were not different or unexpected. Further analyses of the BASIL-2 dataset and other similar cohorts of patients with chronic limb-threatening ischaemia will be required to understand the reasons for the differences observed. However, differences in time to first revascularisation, the timing and nature of additional procedures, and in best medical therapy might be important.[14,27,28] BASIL-2 recruitment was stopped early due to the COVID-19 pandemic. COVID-19 also had a major adverse effect on follow-up, particularly for endpoints that required face-to-face assessment. However, we see no evidence that the observed difference in outcomes between the groups is associated with COVID-19.

In 2012, when the BASIL-2 trial was being developed, a vein bypass first revascularisation strategy was hypothesised to be superior to a best endovascular

treatment first strategy. This was mainly based on the results of the BASIL-1 trial.[14] However, only around 25% of participants in the BASIL-1 trial had an infra-popliteal revascularisation. This reflected the fact that at the time (1999–2004) most patients with chronic limb-threatening ischaemia were having only more proximal (mainly femoro-popliteal) infra-inguinal procedures.

In patients with, often heavily calcified, infra-popliteal disease both vein bypass and best endovascular treatment remain technically challenging, despite advances in endovascular techniques and devices. As a result, controversy remains as to whether patients with chronic limb-threatening ischaemia requiring an infra-popliteal revascularisation and who are suitable for both procedures should be offered vein bypass or best endovascular treatment first.[29]

At first glance, our results appear to conflict with the BEST-CLI trial,[18] which showed that a vein bypass first revascularisation strategy using optimum (single segment great saphenous) vein was associated with a better outcome, in terms of a composite primary outcome of major adverse limb event or death, than an endovascular first revascularisation strategy. There were no differences in outcome in participants who did not have an optimal vein for bypass.[18] However, there are many differences between the two trials, including the primary endpoint. Our clinical experience suggests that few patients with chronic limb-threatening ischaemia are deemed suitable and have an optimal vein for infra-popliteal bypass. Future work is required to determine whether the patients enrolled in BASIL-2 are more like the patients with a non-optimal vein in the BEST-CLI trial. Although our study and the BEST-CLI trial[18] were developed, run, and analysed entirely independently, we have collaborated closely with the BEST-CLI trial investigators, and we entered into a data sharing agreement with them before either trial was analysed. The data sharing agreement will allow an in-depth comparison of the two trials that will hopefully explain why some of the outcomes observed appear to be different. One of the outputs will be an individual-patient-level data meta-analysis. Until this work is completed, we can only speculate as to why the two trials appear to have reached different conclusions.

Outcomes for the patients in the BASIL-2 trial were poor (median amputation-free survival of 3·8 years [IQR 3·1–4·4]; vein bypass group 3·3 years [2·1–4·3]; best endovascular treatment group 4·4 [3·4–5·9]) and not materially different from those reported in the BASIL-1 trial.[30] In both trials, around half of the patients had died by 5 years after randomisation. The limb salvage rates of around 80% at 5 years observed in both trials are probably because many patients died and were not at risk of limb loss.[31]

At randomisation, most patients in the BASIL-2 trial were on what has been termed best medical therapy. The severe multilevel atherosclerotic disease that causes chronic limb-threatening ischaemia develops over many years. We do not have information on the quality of previous best medical therapy and lifestyle (eg, stop smoking) interventions. Randomisation with minimisation, as we have described, ensures that variations in the quality of previous best medical therapy and lifestyle interventions will be equally represented in both groups. Around 20% of patients admitted that they were still smoking and around 70% of patients had

	Vein bypass group (n=172)	Best endovascular treatment group (n=173)	Mean Difference (95% CI)
Visual analogue scale			
1 month	3·9 (3·0; 122 patients)	4·0 (3·0; 129 patients)	−0·22* (−0·98 to 0·49)
12 months	3·1 (3·1; 98 patients)	3·7 (3·0; 98 patients)	−0·15* (−0·94 to 0·63)
24 months	2·9 (2·8; 70 patients)	3·2 (2·8; 83 patients)	−0·13* (−0·99 to 0·73)
Vascular Quality of Life Questionnaire composite total score			
1 month	4·1 (1·6; 116 patients)	4·1 (1·4; 116 patients)	−0·02† (−0·39 to 0·35)
12 months	4·7 (1·6; 91 patients)	4·5 (1·5; 95 patients)	0·00† (−0·40 to 0·40)
24 months	4·8 (1·4; 64 patients)	4·6 (1·4; 72 patients)	0·11† (−0·34 to 0·56)
EQ5D5L health state score			
1 month	60·5 (22·1; 130 patients)	64·5 (19·7; 137 patients)	−1·66† (−6·72 to 3·40)
12 months	62·4 (23·4; 106 patients)	64·2 (22·9; 100 patients)	−1·63† (−7·26 to 4·00)
24 months	58·5 (22·7; 76 patients)	63·2 (21·6; 85 patients)	−2·98† (−9·19 to 3·22)
EQ5D5L index score (UK participants)			
1 month	0·5 (0·3; 106 patients)	0·5 (0·3; 110 patients)	0·02† (−0·06 to 0·10)
12 months	0·6 (0·3; 86 patients)	0·5 (0·3; 82 patients)	0·02† (−0·07 to 0·11)
24 months	0·5 (0·3; 63 patients)	0·6 (0·3; 65 patients)	0·02† (−0·07 to 0·12)
EQ5D5L index score (Danish and Swedish participants)			
1 month	0·5 (0·4; 24 patients)	0·6 (0·2; 25 patients)	−0·09† (-0·23 to 0·05)
12 months	0·5 (0·3; 19 patients)	0·7 (0·1; 18 patients)	−0·14† (−0·29 to 0·01)
24 months	0·7 (0·2; 13 patients)	0·7 (0·2; 17 patients)	−0·04† (−0·20 to 0·12)
ICEpop CAPability measure for older people			
1 month	0·7 (0·2; 118 patients)	0·7 (0·2; 132 patients)	0·01† (−0·04 to 0·05)
12 months	0·7 (0·2; 100 patients)	0·7 (0·2; 97 patients)	0·01† (−0·04 to 0·07)
24 months	0·8 (0·2; 75 patients)	0·7 (0·2; 80 patients)	0·04† (−0·02 to 0·10)
Short Form-12 Health Survey version 2.0 physical component score			
1 month	33·1 (12·3; 110 patients)	34·9 (10·9; 114 patients)	−0·47† (−3·36 to 2·42)
12 months	37·6 (11·5; 92 patients)	36·0 (11·2; 95 patients)	0·87† (−2·16 to 3·91)
24 months	37·9 (10·7; 70 patients)	36·7 (10·8; 74 patients)	0·52† (−2·84 to 3·88)
Short Form-12 Health Survey version 2.0 mental component score			
1 month	44·8 (8·0; 110 patients)	44·6 (8·8; 114 patients)	−0·27† (−2·43 to 1·90)
12 months	45·9 (8·7; 92 patients)	45·8 (7·1; 95 patients)	−0·08† (−2·39 to 2·23)
24 months	46·3 (7·8; 70 patients)	45·6 (7·5; 74 patients)	−0·28† (−2·92 to 2·35)

Data are mean (SD; n), unless otherwise stated. EQ5D5L=Euroqol 5L. Visual analogue scale scores ranged from 0 to 10: 0=no pain and 10=worst possible pain. Vascular Quality of Life Questionnaire scores ranged from 1 to 7: 1=worst possible health and 7=best possible health. EuroQoL EQ5D5L health state scores ranged from 0 to 100: 0=worst health and 100=best health. EuroQoL EQ5D5L index scores (UK participants) range from −0·59 to 1: 1=perfect health, 0=death, and negative scores imply a health status worse than death (unbearable pain). EuroQoL EQ5D5L index scores (Danish and Swedish participants) ranged from −0·62 to 1: 1=perfect health, 0=death, and negative scores imply a health status worse than death (unbearable pain). ICEpop CAPability measure for older people scores ranged from 0 to 1: 0=absence of capability and 1=full capability. Short Form-12 Health Survey version 2.0 scores ranged from 0 to 100: higher scores indicate better physical and mental health functioning.*Adjusted for minimisation variables, centre, and baseline score; values less than zero favoured the vein bypass group. †Adjusted for minimisation variables, centre, and baseline score; values more than zero favoured the vein bypass group.

Table 3: **Patient reported secondary outcomes**

diabetes, of whom around 50% required insulin. At presentation around 90% of the participants had often quite extensive tissue loss (around 30% had tissue loss alone, and around 60% had tissue loss and pain).[24] These baseline data suggest that there might still be missed opportunities in public health and primary care to prevent chronic limb-threatening ischaemia through medical therapy and lifestyle interventions and missed opportunities to refer patients to secondary care earlier once chronic limb-threatening ischaemia begins to develop.[3,32] Better prevention and timely referral are important: the BASIL-2 trial shows that by the time patients present to vascular and endovascular surgeons and interventional radiologists with established chronic limb-threatening ischaemia, their prognosis is often poor regardless of what form of revascularisation they are offered.[33]

The BASIL-2 trial has some statistical and clinical limitations. The total number of participants we aimed to enrol was not met due to challenges in recruitment. Because the planned sample size was based on the number of events, the reduction in participants was mitigated by increasing the duration of follow-up. Because the study did not reach its planned target event numbers it is important that the uncertainty in the findings is considered. The uncertainty in the estimate is best judged by the point estimate and the confidence interval of the primary endpoint (amputation-free survival; HR 1·35 [95% CI 1·02–1·80]): an increase in risk of 35% (HR 1·35) is the most likely value, with increases in risk of 2% (HR 1·02) and 80% (HR 1·80) the least probable points in this range. Although most of this range covers the point estimates likely to be considered clinically important differences, it also includes smaller differences. However, the possibility that a vein bypass first could be more effective than best endovascular treatment first revascularisation strategy in this patient cohort is very unlikely.

Clinical colleagues will need to consider some important issues when deciding to what extent our findings can be applied to their patients, practice, and health-care system. Vascular specialists in some countries might be unable to offer best endovascular treatment due to cost.[34] Patients with chronic limb-threatening ischaemia presenting in other countries might be different in several ways (eg, age, sex, prevalence of risk factors, and racial background).[4,18] Many patients with chronic limb-threatening ischaemia are offered primary amputation or conservative (end of life) care rather than revascularisation; many patients do not have a suitable vein for vein bypass, so they are deemed only suitable for best endovascular treatment; and even patients who are deemed suitable for vein bypass and have a good vein might choose the less invasive endovascular option.[4]

Apart from the central site at the University of Birmingham, Birmingham, UK, collecting reliable screening data proved impossible due to changes in the funding model and the need to increase in the number of centres. However, in Birmingham, we established the BASIL prospective cohort study, which includes all patients (n=471) with chronic limb-threatening ischaemia admitted to Heartlands Hospital, Birmingham, UK, between June 24, 2014 and July 31, 2018. These data will be reported separately. We hope the prospective cohort study will allow the findings of the BASIL-2 trial to be viewed in the context of patients with chronic limb-threatening ischaemia as a whole and help establish the generalisability of the BASIL-2 trial to similar patients who were not recruited to the trial.

Recruiting patients to the BASIL-2 trial was much more difficult than anticipated. The BEST-CLI trial[18] also faced similar difficulties despite increased funding and a larger potential patient population.

As well as many patients being deemed unsuitable for both procedures (especially for vein bypass) for a variety of reasons, an absence of equipoise on the part of clinicians and patients was an important issue. Colleagues explained it was often easier to offer early best endovascular treatment than it was to offer early vein bypass and easier to obtain imaging confirming suitability for best endovascular treatment. These logistical issues might cause delay to revascularisation, which can be associated with a worse outcome.[35] In the BASIL-2 trial, most patients received their allocated revascularisation procedures in a timely manner that was clinically appropriate for that individual. Nevertheless, the BASIL-2 trial is a pragmatic randomised trial that compares two different revascularisation strategies, rather than two different sets of procedures, in a real-world context of what can be realistically achieved within the national, publicly funded health-care systems of the UK, Sweden, and Denmark. It is important that the BASIL-2 primary comparative analysis be done and the results interpreted on an intention-to-treat basis because results in alternative analysis populations might provide biased estimates (since randomisation can no longer preserve balance for known risk factors).

In conclusion, the BASIL-2 trial shows that a vein bypass first revascularisation strategy led to a 35% increased risk of major amputation or death in patients with chronic limb-threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularisation procedure to restore limb perfusion compared with a best endovascular treatment first revascularisation strategy. This difference was mainly driven by fewer deaths in the best endovascular treatment first revascularisation group as limb-based outcomes were similar between the two groups.

Contributors

AWB was the chief investigator and responsible for all aspects of study design, completion, and dissemination. CAM and JH were responsible for the analysis of the trial data and co-authored this manuscript. MP and LM recruited and followed up patients, collected, verified, and interpreted the data, and were members of trial management and writing groups. GRB designed the protocol and Case Record Form, was a member of the trial management group, recruited and followed up patients, interpreted the data, and was a member of the writing group. IC, AD, AG, SH, KH,

JM, JVP, STR, AS, DJAS, and HZ recruited and followed up patients, interpreted the data, and were members of writing group. HJ designed the data collection methods and tools, designed the protocol, had oversight and leadership responsibility for the trial management group, collected the data, was a project administrator, and was a member of writing group. LK designed the CRF, recruited and followed up patients, collected, verified, and interpreted the data, and was a member of the writing group. SL was a project administrator and curated the data. SP obtained funding for the trial, designed the trial, oversaw the running of the trial, developed and led on the statistical aspects of the study, and supervised and performed the interim analyses. GS had oversight of and led the research activity planning and execution, and prepared, created, and presented the published work. JJD designed the study, analyses and interpreted the data, and was a member of the writing group. We confirm that all authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. CAM and JH verified the underlying data reported in the manuscript.

Declaration of interests

AWB reports salary part paid by a National Institute for Health (NIHR) and Care Research Health Technology Assessment (HTA) BASIL-2 grant; payment expert advice and testimony from NHS Resolution, His Majesty's Coroners, National Crime Agency, UK, Scotland, Wales, and Northern Ireland Governments, and various law firms, outside of the submitted work; and payment to his institution and personal honoraria for committee work from NIHR HTA and NICE. GRB reports salary part paid by a NIHR HTA BASIL-2 grant; the BASIL-2 grant also paid mileage for visiting patients in the BASIL-2 trial for follow-up assessments. AD reports honoraria from Boston Scientific, Cordis, Medalliance, and Abbott. KH reports honoraria from Le Maitre and Bayer. STR reports payment for expert testimony from McCollum Consultants; consulting fees from 3M, Bayer, and Avita; speaker fees from 3M, Bayer, Avita, and Terumo; travel support Bayer and Terumo; and is an advisory board member for 3M, Bayer, and Avita. AS reports honoraria and institutional grant support from Shockwave and Abbott and unpaid committee work for NICE. HZ reports an institutional grant from Abbott and honoraria from Limflow, Abbott, Boston Scientific, Bentley, Cook Medical, and Medtronic.
All other authors declare no competing interests.

Data sharing

Requests for data should be directed to the corresponding author. Patient-level data will be made available within 6 months of publication. Requests will be assessed for scientific rigour before being granted. Data will be anonymised and securely transferred. A data-sharing agreement might be required. The BASIL-2 investigators already have a data sharing agreement with the BEST-CLI trial investigators.

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