Vein bypass first vs. best endovascular treatment first revascularisation strategy for chronic limb-threatening ischaemia due to infra-popliteal disease: the BASIL-2 RCT

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Scientific summary

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Scientific summary

Background

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

Objectives

The primary objective of the study was to examine the effectiveness and cost-effectiveness of using a VB-first compared to a BET-first revascularisation strategy in terms of preventing major (above the ankle) amputation or death from any cause [amputation-free survival (AFS)] in patients with CLTI who required an IP, with or without an additional more proximal infra-inguinal revascularisation procedure, to restore limb perfusion.

Design

Superiority, open-label, pragmatic, multicentre, phase III randomised trial.

Setting

Thirty-nine vascular surgery units in the United Kingdom, and one each in Sweden and Denmark.

Participants

Those with CLTI due to atherosclerotic PAD and who required an IP revascularisation, with or without an additional more proximal infra-inguinal revascularisation procedure, to restore limb perfusion.

Interventions

A VB-first or a BET-first IP, with or without an additional more proximal infra-inguinal revascularisation strategy, to restore limb perfusion. Most VBs were constructed with 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.

Outcome measures

The primary outcome was AFS defined as time to first major (above the ankle) amputation or death from any cause. Secondary outcomes included: time to death from any cause (overall survival); time to major amputation of the trial leg; major adverse limb event (defined as major amputation of the trial leg, or any further major revascularisation intervention to the trial leg, following the first revascularisation

intervention); major adverse cardiac event (defined as chronic limb-threatening ischaemia and/or major amputation affecting the non-trial leg, myocardial infarction, transient ischaemic attack or stroke); 30-day morbidity and mortality; relief of ischaemic pain as determined by visual analogue scale and opiate usage; health- related quality of life using generic [EuroQol-5 Dimensions, five-level version (EQ-5D-5L), Short Form questionnaire-12 items, ICEpop CAPability measure for Older people] and disease-specific (the Vascular Quality of Life Questionnaire) tools; further major revascularisation intervention to the trial leg (following the first revascularisation intervention); re-intervention and crossover intervention (where re-intervention is defined as the same, and a crossover procedure is defined as an alternative, revascularisation procedure to the first revascularisation procedure post-randomisation); healing of tissue loss (ulcers, gangrene) at or below the ankle presumed to be caused by PAD as assessed by the perfusion, extent, depth, infection and sensation score, the Wound Ischaemia and foot Infection tool; and haemodynamic measurements (ankle–brachial pressure index, and toe brachial pressure index). Serious adverse events were collected up to 30 days post first revascularisation. Economic evaluation analyses in the form of cost-effectiveness and cost–utility analysis (CUA) were conducted from the perspective of the UK NHS alongside the trial. The base case analyses considered only hospital costs and an additional scenario and subgroup analyses were carried out.

Sample size

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. Based on the Bypass versus Angioplasty in Severe Ischaemia of the Leg Trial (BASIL-1) trial. AFS 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 AFS of one-third [hazard ratio (HR) 0.66] at the 5% significance level. 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 randomised participants 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 participant. The modelling was updated approximately every 6 months based on emerging data.

Results

Between 22 July 2014 and 30 November 2020, 345 participants were randomised, 172 to the VB-first group and 173 to the BET-first group. The baseline characteristics of the two groups were similar. Major amputation or death occurred in 108 (63%) of 172 patients in the VB-first group and 92 (53%) of 173 patients in the BET-first group {adjusted HR 1.35 [95% confidence interval (CI) 1.02 to 1.80]; $p = 0.037$}. Ninety-one (53%) of 172 patients in the VB-first group and 77 (45%) of 173 patients in the BET-first group died [adjusted HR 1.37 (95% CI 1.00 to 1.87)]. In both groups the commonest causes of morbidity and mortality, including those occurring within 30 days of their first revascularisation, were cardiovascular and respiratory events. Over follow-up, the economic evaluation results showed that BET-first was associated with £1690 less hospital costs compared to VB-first with additional survival without amputation. The cost utility analysis showed that compared to VB-first, BET-first was associated with £2524 and £2233 less hospital costs and 0.016 and 0.085 QALY gain after 2 and 3 years from randomisation.

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Conclusions

In the BASIL-2 trial, a BET-first revascularisation strategy was associated with a better AFS, which was largely driven by fewer deaths in the BET-first group. In both the CUA and cost-effectiveness analysis (CEA) analyses and from a NHS and societal perspective BET-first dominated VB-first and is therefore a highly cost-effective intervention for the NHS. These data suggest a greater role for BET in the management of patients with CLTI who require an IP revascularisation to restore limb perfusion.

In patients with CLTI who required an IP, with or without an additional more proximal infra-inguinal revascularisation procedure, to restore limb perfusion, a BET-first revascularisation strategy was associated with reduced hospital costs (£1690) and improved AFS (0.429 years), out to 7 years following randomisation. BET-first therefore dominated VB-first in the CEA. Similarly, in the health-related quality of life the CUA, BET-first was cost-saving with improved QALYs (£2524 and £2233 less hospital costs and 0.016 and 0.085 more QALYs at 2 and 3 years, respectively) and so dominated VB-first. This economic analysis therefore shows that BET-first is a cost-effective option from an NHS and societal perspective. The sensitivity analysis supported the base-case analysis and BET-first was found to be cost-effective at different willingness-to-pay thresholds. Similar findings were found in all other scenario analyses when considering costs of primary and other hospital healthcare services, taking a broader societal perspective, which includes out-of-pocket expenditure and the costs associated with productivity loss, patient's adherence to study protocol, the impact of imputation by focusing on participants with complete hospital cost and EQ-5D-5L data only. However, these findings should be interpreted cautiously given the large number of imputed cost values and the substantial probability of a very small QALY difference.

Study registration

Current Controlled Trials ISRCTN27728689.

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