

Multicentre randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial

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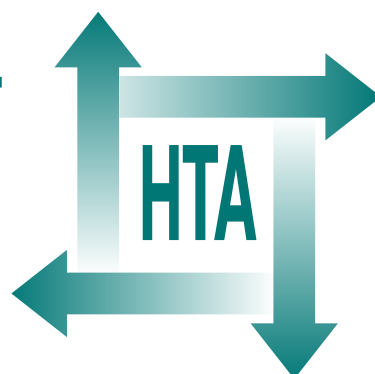
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Executive summary

Health Technology Assessment 2010; Vol. 14: No. 14
DOI: 10.3310/hta14140

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk





Executive summary

Introduction

The numbers of patients requiring lower limb revascularisation for severe limb ischaemia (SLI) are likely to increase significantly worldwide as a result of ageing populations, the increasing prevalence of diabetes, and the failure so far to significantly reduce global tobacco consumption. The two principal treatment alternatives – bypass surgery and balloon angioplasty – have generally been considered to have a number of possible relative advantages and disadvantages. Previous studies that have attempted to compare them have all had serious methodological limitations. The resulting absence of evidence means controversy continues as to which is associated with a better clinical outcome and is a more effective use of health-care resources.

Objectives

The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial compared for the first time, in a multicentre randomised controlled trial (RCT), a 'bypass-surgery-first' with a 'balloon-angioplasty-first' revascularisation strategy in patients with SLI due to infrainguinal disease who required immediate/early revascularisation. The main outcomes were amputation-free survival (AFS), overall survival (OS), health-related quality of life (HRQoL) and the cost-effective use of hospital resources.

Methods

Before the trial we undertook a Delphi consensus study of vascular surgeons' and interventional radiologists' views on the treatment of SLI. Between August 1999 and June 2004 we randomised 228 patients to a bypass-surgery-first and 224 to balloon-angioplasty-first revascularisation strategy in 27 UK hospitals. We scored preintervention angiograms using the Bollinger and Transatlantic Society Consensus (TASC) II methods; undertook an audit to assess trial generalisability; measured self-reported generic and disease-specific HRQoL out to 36 months; and obtained patient-specific data on hospital resource use and costs. The trial

received ethical approval and was registered with the National Research Register (NRR) and the International Standard Randomised Controlled Trials Number Scheme (ISRCTN45398889). All patients provided written informed consent. Follow-up data were obtained from dedicated research nurses; the Information and Statistics Division of the NHS in Scotland using record linkage to Scottish Morbidity Records and the General Registrar Office (Scotland); the Office of National Statistics in England; paper and electronic hospital records; and general practitioners.

Results

Overview

The Delphi studies revealed substantial disagreement between and among vascular surgeons and interventional radiologists with regard to the appropriateness of bypass surgery or balloon angioplasty for SLI due to infrainguinal disease. Half of patients presenting to the top six recruiting centres with SLI underwent immediate/early revascularisation. Of these, approximately 30% were eligible for randomisation in that they were considered suitable for bypass and angioplasty within the 'grey area of clinical equipoise' and *c.* 70% of these entered the trial. Trial patients were well matched in terms of baseline clinical characteristics, angiographic severity and extent of disease. Over 40% of patients had diabetes; over a third were still smoking; three-quarters had tissue loss; over a half had a highest ankle pressure < 50 mmHg; a quarter had bilateral SLI; and most were elderly with a significant cardiovascular past medical history. Despite this, at the time of referral to vascular services, a third of patients were not receiving an antiplatelet agent and only a third of patients were receiving a statin. A quarter of bypasses involved prosthetic material; 90% of vein grafts were constructed using the great saphenous vein; and the distal anastomoses were fashioned in approximately equal numbers at the above-knee popliteal, below-knee popliteal, and crural arteries. With regard to angioplasty, in *c.* 70% of patients interventional radiologists attempted to treat a single length of disease; in the remainder, attempts were made to treat several (up to four) separate disease lengths. The numbers of transluminal

and subintimal angioplasties were approximately equal with just over 10% being reported as mixed. Approximately 80% of the angioplasty patients underwent treatment of the superficial femoral artery either alone (*c.* 40%) or in combination with the popliteal artery (*c.* 40%) and crural arteries (*c.* 20%). Most of the remaining patients underwent treatment of the popliteal segments either alone or more usually in combination with crural arteries; the number of isolated crural artery balloon angioplasties was small.

Interim intention-to-treat analysis – 2005

Following randomisation, 195/228 (86%) bypass surgery and 216/224 (96%) balloon angioplasty patients underwent an attempt at their allocated treatment at a median (interquartile range) of 6 (3–16) and 6 (2–20) days respectively. Surgery was associated with significantly lower immediate failure (3% versus 20%), higher 30-day morbidity (57% versus 41%) and lower 12-month reintervention (18% versus 26%) rates than angioplasty. The 30-day mortality was similar (surgery 5%, angioplasty 3%). By 2005, 99% of patients had been followed up for 1 year and 48% for 3 years; 248 (55%) patients were alive with their trial leg intact; 38 (8%) were alive with their trial leg amputated; 36 (8%) had died subsequent to amputation; and 130 (29%) had died with their trial leg intact. Overall AFS at 1 and 3 years was not significantly different; 68% and 57% for bypass surgery and 71% and 52% for balloon angioplasty. However, a post-hoc analysis found a significantly reduced hazard in terms of AFS [adjusted hazard ratio (HR) 0.37; 95% CI 0.17 to 0.77; $p = 0.008$] and OS (adjusted HR 0.34; 95% CI 0.17 to 0.71; $p = 0.004$) for surgery relative to angioplasty beyond 2 years from randomisation.

Final intention-to-treat analysis – 2008

For the 2008 analysis, apart from four participants lost to follow-up, 100% of patients had been followed for 3 years and 54% for more than 5 years; the longest follow-up was over 7 years; 250 patients (56%) were dead; 168 (38%) were alive without amputation; and 30 (7%) were alive with amputation. Considering the follow-up period as a whole, AFS and OS did not differ between randomised treatments. However, for those patients surviving beyond 2 years from randomisation, bypass surgery was associated with a reduced HR for subsequent AFS (HR 0.85; 95% CI 0.5 to 1.07;

$p = 0.108$) and for subsequent OS (HR 0.61; 95% CI 0.50 to 0.75; $p = 0.009$) in an adjusted, time-dependent Cox proportional hazards model. This equates to an increase in subsequent restricted mean OS of 7.3 months (95% CI 1.2 months to 13.4 months; $p = 0.02$) and an increase in restricted mean AFS of 5.9 months (95% CI 0.2 months to 12.0 months, $p = 0.06$) during the subsequent mean (range) follow-up of 3.1 years (1 to 5.7 years). Vein bypasses performed better than prosthetic bypasses ($p < 0.01$ for AFS, $p = 0.11$ for OS, log-rank tests). There were no differences between transluminal and subintimal angioplasty. Prosthetic bypass performed worse than angioplasty. Patients who underwent bypass surgery after failed angioplasty fared significantly worse than those who underwent bypass surgery as their first treatment. A prognostic model based on age; presence of tissue loss; smoking; a history of angina, myocardial infarction, stroke or transient ischaemic attack; serum creatinine; below-knee Bollinger angiogram score; body mass index; number of recordable ankle pressures; and highest ankle pressure was highly predictive of survival beyond 2 years from randomisation. HRQoL was non-significantly better in the surgery group before and after randomisation. Amputation was associated with a significant reduction in HRQoL. Over the first year, hospital costs in patients randomised to surgery (£22,002 total, £18,369 hospital stay, £3635 procedure) were significantly higher (difference £5420; 95% CI £1547 to £9294) than those (£16,582 total, £14,468 hospital stay, £2115 procedure) for patients randomised to angioplasty. This decreased to £3533 (£29,006 surgery versus £25,472 angioplasty, not significant) by the end of year 3 and to £2310 (£33,539 surgery versus £31,228 angioplasty, not significant) by the end of year 7. After 3 years, procedure costs accounted for 9% and 14% of total costs in the angioplasty and surgery groups respectively; most of these were incurred in the first year. The average number of hospital stays for both groups was four and average length of stay was just over 2 months (71 days). On average, BASIL patients spent 5–6 weeks of their first post-randomisation year in hospital and then 2–3 weeks per year thereafter. Most of this was in the wards and not in high-dependency units (HDUs) or intensive-therapy units (ITUs). Patients randomised to surgery used around a half day more of HDU and a few more hours of ITU than those randomised to angioplasty. A 7-year (non-quality-adjusted) perspective shows that patients randomised to surgery live, on average, 29 days longer (41 days longer with their trial leg intact) at an additional average cost of £2310.

This equates to £29,095 per additional year of OS and £20,579 per additional year of AFS. A 36-month quality-adjusted perspective generates a mean quality-adjusted life time of 442 days for angioplasty and 452 days for surgery (mean difference 10 days; 95% CI –48 days to 68 days; not significant) at an estimated additional average hospital cost of £3533. The 3-year point estimate for the cost-effectiveness of surgery compared with angioplasty [cost per quality-adjusted life-year (QALY)] is therefore estimated at £125,499. The cost-effectiveness acceptability curve for AFS is relatively flat beyond the point estimate (£20,579), indicating a substantial possibility that surgery may be cost-ineffective at broadly accepted willingness-to-pay thresholds.

Implications for practice

The greatest gains in SLI lie in early diagnosis, best medical therapy and prompt referral. Most BASIL patients had developed SLI slowly over months, often years. Despite this, and being at exceptionally high overall cardiovascular risk, many patients:

- had never received ‘best medical therapy’ for their multisystem atherosclerotic disease
- were referred (too) late to vascular services for (successful) revascularisation
- were far from medically optimised at the time of referral.

It seems likely, therefore, that public-health and primary- and secondary-care measures aimed at:

- detecting lower limb arterial disease at an earlier stage (before it becomes life and limb threatening)
- ensuring that all such patients are offered evidenced-based ‘best medical therapy’
- encouraging prompt referral to vascular services for specialist care

would significantly diminish the burden imposed by SLI on the health of the nation.

Multidisciplinary team working

BASIL strongly suggests that the best outcomes for SLI are achieved when vascular surgeons and interventional radiologists work closely together with other professionals as part of a multidisciplinary team in specialist, high-volume centres (www.vascularsociety.org.uk/).

Treatment recommendations based on BASIL trial results

The findings of our study suggest that in patients with SLI due to infrainguinal disease the decision whether to perform bypass surgery or balloon angioplasty first appears to depend upon life expectancy. Patients expected to live less than 2 years should usually be offered balloon angioplasty first as it is associated with less morbidity and cost, and such patients are unlikely to enjoy the longer-term benefits of surgery. By contrast, those patients expected to live beyond 2 years should usually be offered bypass surgery first, especially where a vein is available as a conduit.

Role of prosthetic bypass in the management of SLI

Many patients who could not undergo a vein bypass would probably have been better served by a first attempt at balloon angioplasty than prosthetic bypass. Surgeons should make every effort to use vein and should view prosthetic material as a last resort.

Role of balloon angioplasty in the management of SLI

The immediate technical and early clinical failure rate of angioplasty in SLI is high (*c.* 25%) and patients who underwent bypass surgery after failed angioplasty fared significantly worse than those who underwent surgery as their first procedure. So, angioplasty does not appear to be a ‘free shot’ as has often been claimed. Whether failed angioplasty selects patients who were going to do badly whatever treatment they received, or whether angioplasty *per se* reduces the chances of successful surgical revascularisation, these data should be borne in mind when considering treatment options.

The role of amputation and the care of vascular amputees

In retrospect, the interests of a significant proportion of BASIL patients would have been best served by primary amputation, followed by high-quality rehabilitation, rather than often repeated and ultimately unsuccessful attempts at revascularisation. Amputees tended to spend long periods on acute surgical wards where they consumed expensive acute resources while not receiving the rehabilitation they required. There would seem to be a need to rethink services for vascular amputees so that the available resources

can be used in a more clinically and cost-effective manner.

Summary of research recommendations

We suggest that further research is required to:

- repeat the Delphi studies to determine whether there has been any convergence of views as to the relative merits of bypass surgery and balloon angioplasty in SLI
- confirm or refute the BASIL findings and recommendations in further RCTs (we suggest that it is not in the public interest that responsibility for such trials should be left entirely with the private sector where research is understandably driven by commercial interests)
- validate the BASIL trial survival prediction model in a separate cohort of SLI patients
- examine the clinical effectiveness and cost-effectiveness of new endovascular techniques

and devices (such as stents and stent-grafts) in the management of SLI

- compare, within the confines of an RCT, revascularisation versus primary amputation versus best medical and nursing care only in those SLI patients with the poorest prospects.

Trial registration

This trial is registered as ISRCTN45398889.

Publication

Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FGR, Gillespie I, *et al.* Multicentre randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial. *Health Technol Assess* 2010;**14**(14).

NIHR Health Technology Assessment programme

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 96/05/01. The contractual start date was in March 1999. The draft report began editorial review in August 2008 and was accepted for publication in July 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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ISSN 1366-5278

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Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.