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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.

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Abstract

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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Objective: To compare a 'bypass-surgery-first' with a 'balloon-angioplasty-first' revascularisation strategy in patients with severe limb ischaemia (SLI) due to infrainguinal disease requiring immediate/early revascularisation.
Design: A stratified randomised controlled trial. A Delphi consensus study of vascular surgeons' and interventional radiologists' views on SLI treatment was performed before the trial.
Setting: Twenty-seven UK hospitals.
Participants: Patients presenting with SLI as the result of infrainguinal atherosclerosis and who, in the opinion of the responsible consultant vascular surgeon and interventional radiologist, required and were suitable for both surgery and angioplasty.
Interventions: Patients were randomised to either 'bypass-surgery-first' or 'balloon-angioplasty-first' revascularisation strategies.
Main outcome measures: The primary end point was amputation-free survival (AFS); secondary end points were overall survival (OS), health-related quality of life (HRQoL) and cost-effective use of hospital resources.
Results: AFS at 1 and 3 years was not significantly different for surgery and angioplasty. Interim analysis showed that surgery was associated with significantly lower immediate failure, higher 30-day morbidity and lower 12-month reintervention rates than angioplasty; 30-day mortality was similar. Beyond 2 years from randomisation, hazard ratios (HRs) were significantly reduced for both AFS (adjusted HR 0.37; 95% CI 0.17 to 0.77; $p = 0.008$) and OS (HR 0.34; 95% CI 0.17 to 0.71; $p = 0.004$) for surgery relative to angioplasty. By 2008 all but four patients had been followed for 3 years, some for over 7 years: 250 (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 treatments but for patients surviving beyond 2 years from randomisation, bypass was associated with reduced HRs for AFS (HR 0.85; 95% CI 0.50 to 1.07; $p = 0.108$) and OS (HR 0.61; 95% CI 0.50 to 0.75; $p = 0.009$), equating to an increase in restricted mean OS of 7.3 months ($p = 0.02$) and AFS of 5.9 months ($p = 0.06$) during the subsequent follow-up period. Vein bypasses and angioplasties performed better than prosthetic bypasses. HRQoL was non-significantly better in the surgery group; amputation was associated with a significant reduction in HRQoL. Over the first year, hospital costs for bypass were significantly higher (difference £5420; 95% CI £1547 to £9294) than for angioplasty. However, by 3 and at 7 years the differences in cost between the two strategies were no longer significant. Patients randomised to surgery lived, on average, 29 days longer at an additional average cost of £2310. A 36-month perspective showed not significantly different mean

quality-adjusted life times for angioplasty and surgery. The Delphi study revealed substantial disagreement between and among surgeons and radiologists on the appropriateness of bypass surgery or balloon angioplasty.

Conclusions: 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 anticipated 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. 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. The failure rate of angioplasty in SLI is high (*c.* 25%) and patients who underwent bypass after failed angioplasty fared significantly worse than those who underwent surgery as their first procedure. The interests of a significant proportion of BASIL patients may have been best served by primary amputation followed by high-quality rehabilitation. Further research is required to confirm or refute the BASIL findings and recommendations; validate the BASIL survival prediction model in a separate cohort of patients with SLI; examine the clinical and cost-effectiveness of new endovascular techniques and devices; and compare revascularisation with primary amputation and with best medical and nursing care in those SLI patients with the poorest survival prospects.

Trial registration: Current Controlled Trials ISRCTN45398889.

Contents

List of abbreviations

ACM	all-cause mortality
AFS	amputation-free survival
AK	above-knee
BAP	balloon angioplasty
BASIL	Bypass versus Angioplasty in Severe Ischaemia of the Leg
BK	below-knee
BMI	body mass index
BMT	best medical therapy
BSX	bypass surgery
CA	crural artery
CLI	critical limb ischaemia
Di-AT	distal anterior tibial (artery)
Di-Per	distal peroneal (artery)
Di-PT	distal posterior tibial (artery)
Di-SFA	distal superficial femoral artery
ePTFE	expanded polytetrafluoroethylene
EQ-5D	EuroQoL 5D
GRO(S)	General Registrar Office (Scotland)
HDU	high-dependency unit
HR	hazard ratio
HRQoL	health-related quality of life
IA	iliac artery
ISD	Information and Statistics Division of NHS Scotland
ISRCTN	International Standard Randomised Controlled Trials Number
ITU	intensive-therapy unit
LSV	long saphenous vein
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
ONS	Office for National Statistics
OS	overall survival
PA	popliteal artery
PEP	primary end point
PFA	profunda femoris artery (deep femoral artery)
Pr-AT	proximal anterior tibial (artery)
Pr-Per	proximal peroneal (artery)
Pr-PT	proximal posterior tibial (artery)
Pr-SFA	proximal superficial femoral artery
PTA	percutaneous transluminal angioplasty
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
SCLI	subcritical limb ischaemia
SF-36	Short Form 36
SF-6D	Short Form 6D
SFA	superficial femoral artery
SLI	severe limb ischaemia
SMR1	Scottish Morbidity Records
TASC II	Trans-Atlantic Society Consensus II
TPT	tibioperoneal trunk
VascuQoL	Vascular Quality of Life Questionnaire
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

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.

Chapter 1
Introduction

In most developed countries the incidence of severe limb ischaemia (SLI), characterised by the presence of rest/night pain and tissue loss (ulceration, gangrene), is estimated to be 50–100/100,000 per year and leads to significant morbidity and mortality as well as to the consumption of considerable health-care and social-care resources.[1] Our ageing populations, the increasing prevalence of diabetes and its lower-limb complications,[2] and the failure to significantly reduce global tobacco consumption mean that, despite advances in medical therapies,[3] the numbers of patients requiring lower-limb revascularisation for SLI in developed, and increasingly in developing, countries is likely to increase in the foreseeable future.

The two currently available treatments, bypass surgery and balloon angioplasty, are generally considered to have a number of relative advantages and disadvantages (Table 1).[4–19]

Previous studies, including randomised controlled trials (RCTs),[5,6,20] and large hospital[21,22] and population-based[23] surveys, have attempted to compare the clinical effectiveness and cost-effectiveness of these two treatments. However, all have had one or more major methodological problems.[16] These include: a lack of controls; small patient numbers; poorly defined patients and interventions; the inclusion, comparison and combined analysis of patients with intermittent claudication and SLI as well as patients with aortoiliac and infrainguinal disease; retrospective analysis; and short and/or incomplete follow-up.[5,18–20,24–31]

The resulting absence of evidence[32,33] has led to continuing uncertainty as to whether bypass surgery or balloon angioplasty is associated with a better clinical outcome, and a more effective use of health-care resources, in patients whose leg is threatened by SLI and who are potentially suitable for both treatments.[34–38]

TABLE 1 *The potential advantages and disadvantages of bypass surgery and balloon angioplasty as a first-line treatment for SLI due to infrainguinal disease*

	Bypass surgery	Balloon angioplasty
Pros	Superior long-term anatomic patency and clinical durability[4–6]	Low morbidity and mortality and requirement for urgent surgical intervention[7]
		Low cost
		Quick to perform
		Shorter hospital stay
		Can be repeated
		Failed angioplasty may not jeopardise subsequent surgery[7]
		Preserves collaterals so that even if the angioplasty site occludes symptoms may not return and tissue loss may remain healed[8,9]
Cons	Significant morbidity and mortality[10]	Limited anatomic and haemodynamic patency and clinical durability[14]
	Significant resource utilisation (theatre time and personnel, prolonged hospital stay)	Only a minority of patients may be suitable, especially with the transluminal technique[15]
	Graft surveillance, often leading to repeated prophylactic reintervention, required to optimise patency[11,12]	The technique, particularly using the subintimal approach, is technically demanding and satisfactory results may not be widely achievable[16–19]
	Vein as a conduit often unavailable, inadequate in length or poor quality[13]	
	Use of prosthetic material associated with poorer patency and risk of graft infection[4]	

Our aim in instigating the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial was to compare the clinical effectiveness and cost-effectiveness of a 'bypass-surgery-first' with a 'balloon-angioplasty-first' revascularisation strategy in terms of amputation-free survival (AFS), all-cause mortality (ACM), health-related quality of life (HRQoL), post-procedure morbidity and mortality, reinterventions and use of hospital resources.

Chapter 2

The 2005 'interim' main end points analysis

Methods 1999–2005

Recruitment began in August 1999 and finished in June 2004.[39] During this time, 452 patients were randomised at 27 UK hospitals. For 4 years participating centres were supported by six dedicated trial nurses who followed up patients for the first year post randomisation. Data were collated centrally and confidentially at the trial office, which was based at the University Department of Vascular Surgery, Heart of England NHS Foundation Trust, Birmingham, UK.

BASIL audit

The aim of the audit was to determine the proportion of patients randomised into BASIL in relation to the total population of patients presenting with SLI, and to investigate the reasons for non-treatment and non-randomisation of potentially eligible patients. Over a 6-month period (October 2001 to April 2002), approximately halfway through the recruitment period, we prospectively gathered data on all consecutive patients who presented with SLI, and who subsequently underwent diagnostic imaging with a view to revascularisation by either bypass surgery or balloon angioplasty, at one of the six top-recruiting BASIL trial centres. In addition, the responsible consultant vascular surgeons and interventional radiologists were asked to record the reason(s) why, in their opinion, patients were deemed unsuitable for revascularisation or randomisation.

Trial eligibility, randomisation, procedures and follow-up

Participating centres were asked to invite all patients presenting with SLI [defined as rest (night) pain and/or tissue loss (ulceration, gangrene)] as the result of infrainguinal atherosclerosis and who, in the opinion of the responsible consultant vascular surgeon and interventional radiologist, required and were suitable for both bypass surgery and balloon angioplasty to take part in the trial.

All patients provided written informed consent and the study was approved by the Multi-centre Research Ethics Committee for Scotland. The BASIL trial was registered with the National Research Register and the International Standard Randomised Controlled Trials Number Scheme (ISRCTN45398889).

The trial manager, independently of participating centres, randomised patients to either a 'bypass-surgery-first' or a 'balloon-angioplasty-first' revascularisation strategy 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 and supplied to the co-ordinating centre in sealed envelopes.

The referees requested that we respond to their criticism of the use of sealed envelopes: 'Sealed envelopes have been established to be a poor choice of implementation of randomisation. Might be worth commenting that a future trial would use a centralised telephone/web-based randomisation system? Looking at Table 2, despite the authors' reassurances, some of these differences look quite large for a trial of this size, e.g. current smoker 32% versus 40%, previous stroke 18% versus 25%, on antiplatelet 54% versus 62% etc., and the sealed envelopes does make one wonder, probably needlessly, but nevertheless.'

In response, we respectfully submit that:

- sealed envelopes was standard practice when the trial was designed some 10 years ago
- the referees have picked out the extremes from small groupings
- adjusting for these small differences in the analysis made no difference to the results.

Randomisation was stratified by centre, and then by clinical presentation and ankle pressure, into four groups (Figure 1).[40,41]

Centres were encouraged to undertake the allocated procedure as soon as possible after randomisation. The responsible consultant vascular surgeons and interventionalists were permitted to use their normal practice for preintervention assessment, the procedure itself and aftercare. Follow-up data were collected prospectively by research nurses based in the main recruitment

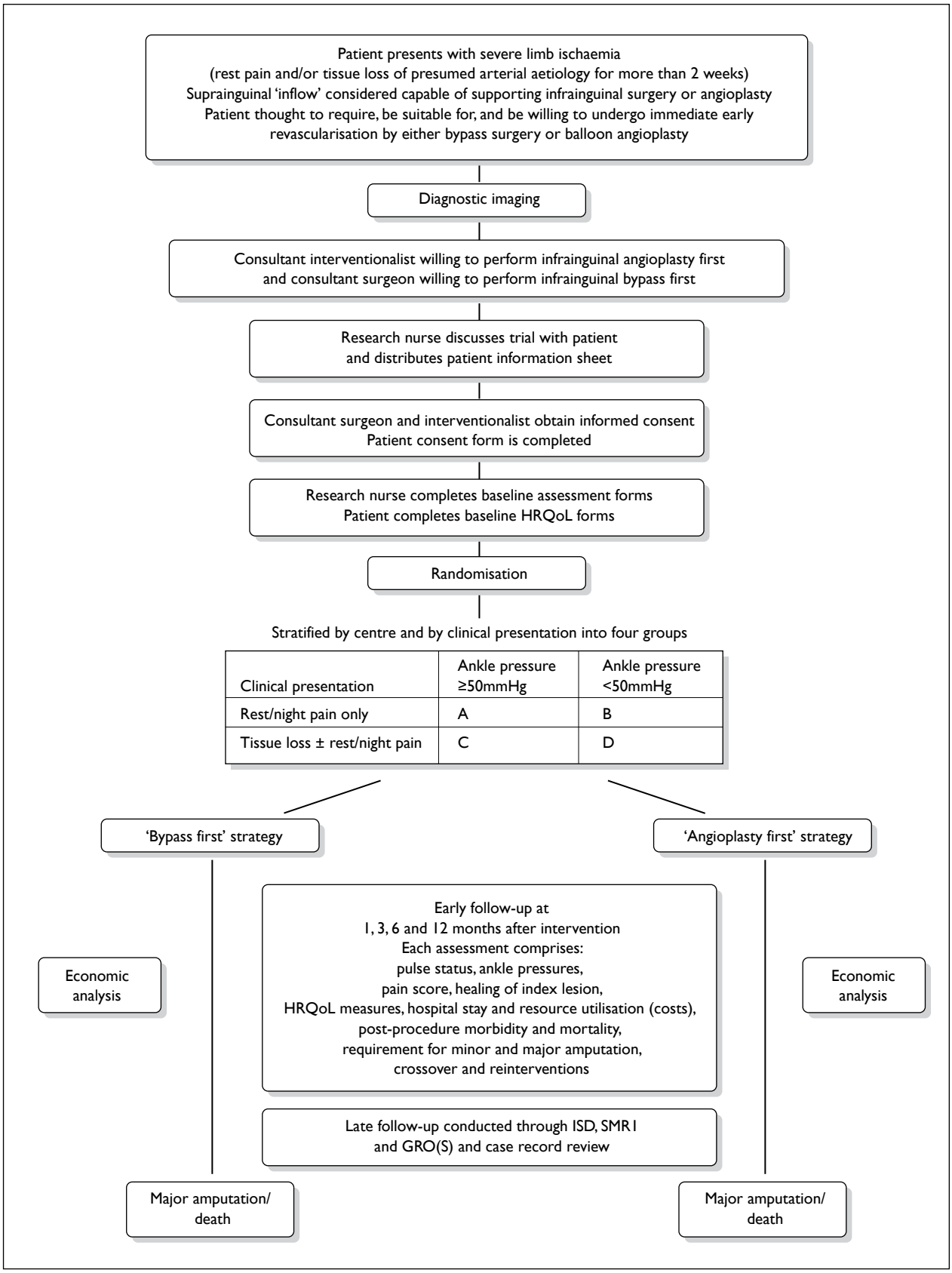


FIGURE 1 *Flow diagram of BASIL trial design.*

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 NHS in Scotland. Notification of death, interventions and discharges from hospital to the end of the trial were provided by using record linkage to Scottish Morbidity Records (SMR1) and General Registrar Office (Scotland) [GRO(S)] death records. Similar information was collected for patients from English centres using data from the Office for National Statistics (ONS) and patient-reported information, which was checked through paper hospital records, electronic hospital information systems and general practitioners. In addition, this prospectively gathered information was cross-checked by reviewing hospital case notes of trial patients at the end of the study.

The primary end point was amputation (of the trial leg at transtibial level or above) -free survival (AFS) and the secondary end points were overall survival (OS) [also known as ACM], post-procedure morbidity and mortality, reinterventions, HRQoL and the use of hospital resources.

The reviewers/editors have requested that we specifically respond to their concern regarding the rationale for including death from any cause as a component of the primary end point (AFS). They ask if nearly all the deaths are related to the underlying disease process being studied (i.e. SLI). They comment further 'Naively, usually relevant cause-specific death is included and non-relevant deaths are either censored at the time of death; or possibly a competing risks type approach is considered?'

We respond as follows. It was decided in about 1998, when the trial was first designed, to include 'all-cause mortality' as an end point because it was considered likely to be a discriminator between the two treatment strategies. That decision has been vindicated by the trial data now available some 10 years later. We would respectfully suggest that 'all-cause mortality' is a more robust, reliable and relevant end point than 'cause-specific mortality'. AFS is the standard end point used in SLI trials (see Chapter 10) and is mandated by the Federal Drug Administration of the USA. Furthermore, competing risk approaches have been criticised as less clinically meaningful in this patient group, many of whom suffer from multiple life-threatening comorbidities.

The reviewers/editors have requested that we respond to their suggestion that 'it is not always clear enough how the authors have dealt with deaths in the secondary outcomes – for example, in the patient-reported outcomes, the deaths seem to have been omitted. Now clearly they will not have values, but it is quite usual to impute floor values or the lowest possible state for those that have died – otherwise the analyses could potentially be biased if there are any imbalances in deaths between the groups.'

This is discussed at greater length in Chapter 7; however, here we respond as follows:

- we believe the methods we have used are more transparent and more relevant to clinical outcomes
- although a potential for bias is always possible it is much lower in a randomised study than might be the case in an observational study because the censoring pattern is the same in both groups
- additionally, in this particular study, any bias would be minimal because mortality differences were small
- the adjusted survival data are used in the calculation of quality-adjusted life-years (QALYs) (taken out to 3 years).
- a standard multiplicative model was used which allows for the utility value reported for each surviving time interval.

Data Monitoring Committee

An independent Data Monitoring Committee met every 6 months during the randomisation period. Having agreed that the stopping rule should be the observation of a highly significant difference in the primary end point (AFS) between the treatment groups ($p < 0.001$), the Data Monitoring Committee agreed to review the trial data 6-monthly, which were prepared for them by independent statisticians, and to make a recommendation to the Steering Committee as to whether the trial should continue. The Data Monitoring Committee also made recommendations to the Steering Committee on the nature and the quality of the data being collected.

Move of trial centre

The reviewers/editors have asked us to respond to their concerns regarding the move of trial office partway through the trial. Specifically, they have commented 'The trial office seems to have moved

from Edinburgh to Birmingham midstream. This happens sometimes, particularly in long trials. What were the issues and how where they overcome? This might be worth a section for the benefit of others facing the same issue.'

We respond as follows. Actually, while somewhat 'inconvenient' in the short term (it probably put the trial back 6–12 months), the move increased the availability of patients from English centres and this made the trial possible. Had the trial remained confined to Scotland (as was originally envisaged) it is unlikely that we would have recruited the number of patients deemed necessary by the power calculation in the time available. The learning point is to engage the largest population (centres/patients) possible from the outset (i.e. always recruit on a national and, if possible, international basis). Such an approach also increases generalisability across the UK; of course at the expense of homogeneity. This tension between inclusivity and purity exists in every large pragmatic RCT and can never be resolved to everyone's satisfaction (this is discussed further in Chapter 10).

Statistical analysis

The sample number calculations proposed that 223 patients per treatment arm would be needed for a 90% power to detect a 15% difference in 3-year AFS at the 5% significance level. This was based on the assumption that the 3-year AFS in one group might be 50% and that in the other group it might be 65%. As discussed above, the primary end point was reached when the trial leg underwent amputation at transtibial level or above (partial foot and digital amputations were not counted as primary end points) or when the patient died of any cause, whichever was sooner. Kaplan–Meier methods were used to construct survival curves on an intention-to-treat basis, using the date of randomisation as time zero.

The statistical analysis was carried out according to a predefined protocol. Survival to the primary end point (amputation of the trial leg or death, AFS) and a secondary end point (ACM or OS) were to be compared by intention to treat. Treatment comparisons were to be survival to 1 year and 3 years from randomisation and hazard rates using a Cox model. The hazard rates were to be compared over the whole time period and separately for events occurring in the first 6 months from randomisation and in the period from 6 months onwards and would be adjusted for a predefined set of covariates. Covariate interactions with treatment would be examined for three specified covariates (stratification group, diabetes and creatinine above/below the median) and also for a risk score calculated from covariates that classified patients according to their hazard of experiencing an end point. All data cleaning and checking of the follow-up data were carried out without reference to the allocated treatment. After the survival curves were examined a further post-hoc analysis was carried out that compared the hazards of the end points restricted to the period after 2 years from randomisation.

Health-related quality of life

We measured self-reported HRQoL using the VascuQoL, EuroQoL 5-D (EQ-5D)[42] and the Short Form 36 (SF-36).[43] These generic measures were collected at baseline (before randomisation) and at 3, 6 and 12 months after randomisation. The EQ-5D responses were converted into a single weighted utility (preference-based) score using the original time trade-off tariff set.[44] The SF-36 items were combined into physical and mental component summary scores using recommended procedures.[45] For all three measures, higher scores indicate better health and well-being as perceived by the patient. Unadjusted differences in mean EQ-5D weighted scores and SF-36 component summary scores were assessed using simple linear regressions. Adjusted differences allowing for baseline scores were based on bias-corrected matching estimators.[46] Further detail on HRQoL methods and analysis is presented in Chapter 6.

Inpatient hospital use and cost

We obtained data on first and all subsequent interventions and hospital stays during follow-up. Patient-specific hospital use was measured using 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. Hospital use was valued using the average cost per inpatient day using the Scottish system of hospital cost statistics.[47] The inpatient hospital cost per day was estimated at £421 for vascular surgical days, £591 for high-dependency unit (HDU) days and £1526 for intensive-therapy unit (ITU) days. The average procedure costs of bypass surgery (£3104) and balloon angioplasty (£1159) were based on estimates in a recent HTA review.[48] Inpatient costs per day and procedure costs are reported on a

price base of financial year 2003–4. Further detail on HRQoL methods and analysis is presented in Chapters 3 and 7.

Results 1999–2005

BASIL audit

This was a prospective audit to determine the numbers of patients presenting with SLI; the proportion of those who were eligible for randomisation within the trial and the proportion of those who were randomised. We also wished to collect data on those who were considered ineligible for randomisation and why; and on those who were considered eligible but were not randomised and why. It was decided for logistical reasons to undertake this audit in the centres that had recruited the most patients to the trial. We decided to conduct the audit approximately halfway through the recruitment period to try to offset any changes in practice, and attitudes to the trial, that may have occurred over this time.

Over a 6-month period (October 2001 to April 2002), approximately halfway through the trial recruitment period, 585 consecutive patients presented with SLI to the top six recruiting centres (who between them recruited 61% of the patients entered into the trial) and underwent diagnostic imaging, usually angiography, with a view to consideration of revascularisation by either bypass surgery or balloon angioplasty (Figure 2). Of these, 129 (22%) required suprainguinal (aortoiliac) intervention and were not, therefore, the subject of the BASIL trial. Of the remaining 456 patients [272 men and 184 women of median (range) age 75 (33–99) years] with SLI due to infrainguinal disease, 220 (48%) were treated conservatively initially without immediate/early revascularisation and 236 (52%) were deemed to require, and be willing to undergo, immediate/early revascularisation. Of these 236 patients, 70 (29%) were considered suitable for randomisation into the BASIL trial because the responsible surgeon and interventionalist agreed that there was equipoise with regard to the preferred first intervention. For the other 166 patients there was a clear preference on the part of the responsible vascular team, or expressed by the patient/family, for either bypass, or angioplasty, or continuing conservative therapy or primary amputation. The responsible consultant vascular surgeons and interventionalists stated that the primary reason for not revascularising or not randomising patients (n = 386) was that: the leg could not be revascularised by either bypass surgery or balloon angioplasty (n = 154, 34%) (non-reconstructable disease); there was significant comorbidity precluding bypass surgery (n = 34, 7%); there had been symptomatic improvement with medical therapy only (n = 14, 3%); the patient was unable to provide informed consent (n = 16, 4%); the patient's pattern of disease was technically unsuitable for balloon angioplasty (n = 75, 16%) or bypass surgery (n = 93, 20%). Note that in many patients there was more than one reason and in many cases the decision was influenced by patient/family wishes. Of the 70 patients deemed suitable for randomisation, 22 refused trial entry and 48 (69%) were randomised.

Trial recruitment, randomisation and follow-up

Consultant vascular surgeons and interventional radiologists from 27 UK hospitals entered 452 patients into the study. A total of 195/228 (86%) patients randomised to bypass surgery and 216/224 (96%) randomised to balloon angioplasty underwent an attempt at their allocated treatment at a median (inter-quartile range) of 6 (3–16) and 6 (2–20) days respectively (not significant, NS). The baseline characteristics of the patients in each group were similar and typical of patients presenting with SLI (Table 2).

Over 40% of the patients were known to have diabetes and over one-third admitted that they were still smoking at the point of randomisation. The great majority of patients had tissue loss and one-quarter had both legs affected by SLI, indicating the advanced nature of the peripheral arterial disease in the trial population. Many of the patients were elderly and most had a significant cardiovascular past medical history. Despite this, one-third of patients were not receiving an antiplatelet agent and only one-third of the patients were receiving a statin at the time they were referred to the vascular service.

The trial ran initially for 5½ years (see Chapter 3 for reporting of extended follow-up). By the close of follow-up on 28 February 2005, 99% of patients had been followed up for 1 year, 74% for 2 years, 48% for 3 years, 22% for 4 years and 8% for 5 years. At the end of this initial (interim) follow-up, 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 having their trial leg amputated and 130 (29%) had died with their trial leg intact.

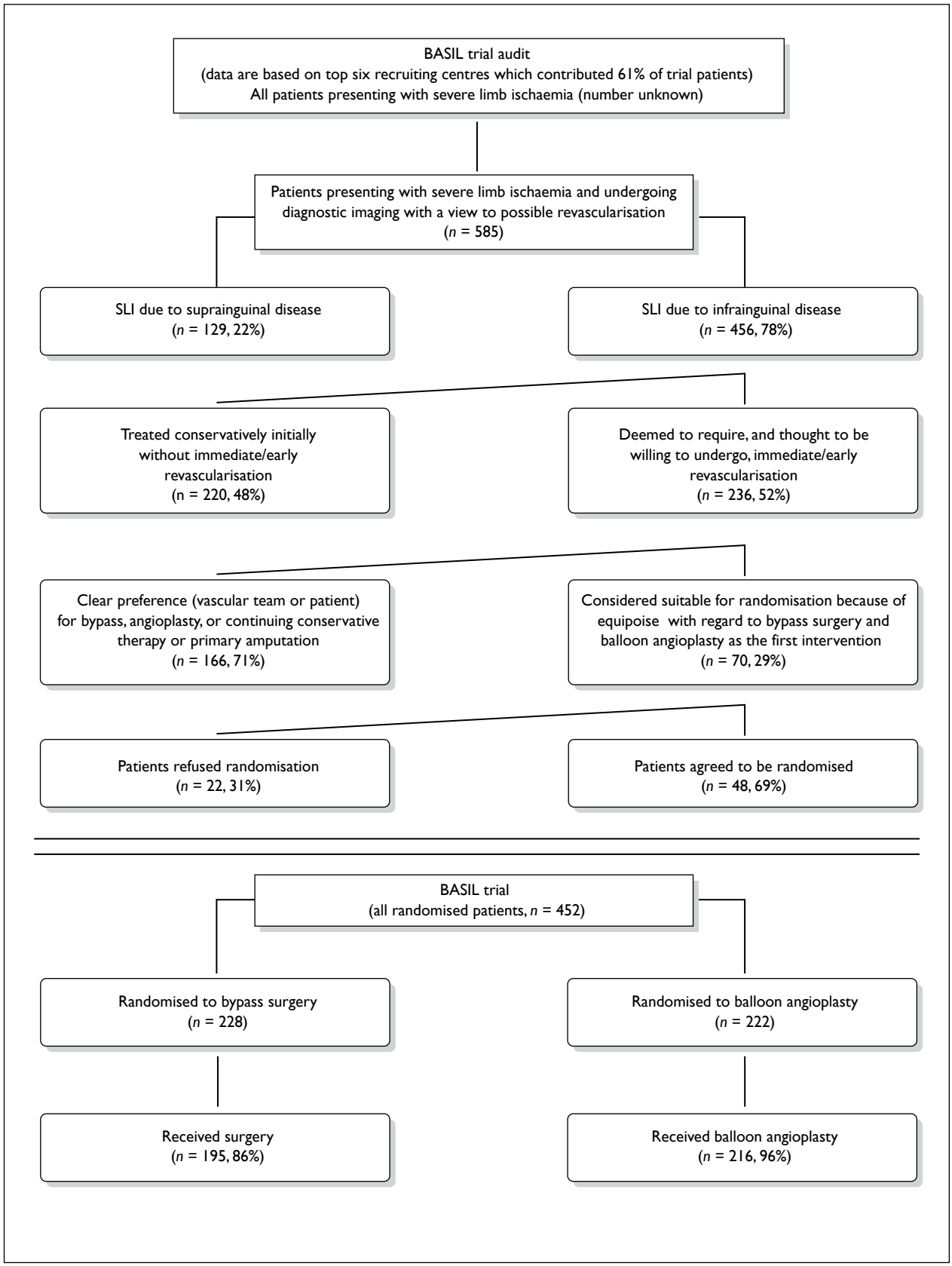


FIGURE 2 *BASIL trial audit: CONSORT diagram showing patient flow into trial.*

TABLE 2 *Baseline characteristics of randomised patients*

Characteristic	Allocated strategy	
	Balloon angioplasty first	**Bypass surgery first**
	n = 224	*n* = 228
Male	57%	62%
Age		
Under 70 years	30%	35%
70–79 years	46%	39%
80 years or more	24%	26%
Trial leg = right	46%	43%
Smoking status		
Never smoked	21%	21%
Current smoker	32%	32%
Ex-smoker (not smoked for > 1 year)	46%	46%
Diabetes		
Not known to be diabetic	58%	58%
Insulin-dependent	17%	17%
Non-insulin-dependent	25%	25%
Angina	19%	18%
Previous myocardial infarction	20%	15%
Previous stroke/transient ischaemic attack	18%	25%
Previous intervention in trial leg	18%	12%
Previous intervention in other leg	16%	21%
Symptomatic arterial disease in other leg?		
No	67%	64%
Yes – intermittent claudication[a]	9%	11%
Yes – severe limb ischaemia	23%	26%
Rest/night pain but no tissue loss in trial leg	24%	27%
Tissue loss (ulcer and/or gangrene) in trial leg	75%	73%
Randomisation stratification group		
Group A: rest/night pain only; ankle pressure ≥ 50 mmHg	20%	21%
Group B: rest/night pain only; ankle pressure < 50 mmHg	4%	6%
Group C: tissue loss ± rest/night pain; ankle pressure ≥ 50 mmHg	48%	50%
Group D: tissue loss ± rest/night pain; ankle pressure < 50 mmHg	27%	23%
On a statin[b]	34%	33%
On drug treatment for hypertension	63%	59%
On antiplatelet agent[c]	54%	62%
Mean creatinine (standard deviation) (μmol/l)	113 (62)	116 (95)

a Intermittent claudication refers to pain in leg on walking but not at rest or at night, with no tissue loss.
b For hypercholesterolaemia.
c In most cases aspirin 75 mg daily.

TABLE 3 *Morbidity and mortality and reinterventions within 30 days of first intervention whether or not that was the treatment allocated at randomisation*

	During the same admission as the first intervention		Following discharge from hospital after first intervention	
	Balloon angioplasty	**Bypass surgery**	**Balloon angioplasty**	**Bypass surgery**
Mortality	7	11	0	0
Morbidity				
Angina	4	4	1	2
Myocardial infarction	6	13	2	2
Stroke	1	3	2	0
Haematoma	14	10	1	5
Haematoma requiring surgical drainage	2	9	0	0
Wound infection	18	45	25	29
Chest infection	4	10	3	2
Urine infection	8	7	2	6
False aneurysm	0	1	0	0
False aneurysm requiring surgical repair	0	1	0	0
Venous thromboembolism	1	0	2	0
Other cardiovascular	0	0	3	2
Gastrointestinal	0	1	2	2
Other	2	1	3	5
Further interventions				
Balloon angioplasty	3	1	1	0
Bypass surgery	21	2	13	0
Above-knee amputation	4	3	0	0
Below-knee amputation	5	3	1	0
Minor amputation	11	11	2	2
Graft 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

Post-procedure (30-day) morbidity, mortality and reintervention

Six patients randomised to bypass surgery and one randomised to balloon angioplasty died before undergoing an intervention. Eleven patients randomised to bypass surgery (5%) and seven to balloon angioplasty (3%) died within 30 days of their first intervention. One patient in each randomised group crossed over and died within 30 days of the alternative procedure so that the 30-day mortality associated with each procedure was the same whether analysed by intention to treat or by first treatment received. A total of 110/195 (57%) patients who were randomised to and underwent attempted bypass surgery as their first procedure and 89/216 (41%) patients who were randomised to and underwent attempted balloon angioplasty as their first procedure had one or more complications within 30 days of their intervention (Table 3). Of these 89 patients, 20 did not develop their complication until after they had gone on to have bypass surgery as a second procedure after a failed balloon angioplasty as a first procedure.

Patients randomised to surgery: early (12-month) follow-up

Of the 228 patients randomised to bypass surgery, 195 underwent attempted bypass surgery (Figure 3). Of these, five underwent a successful endarterectomy and vein patch rather than a bypass. Two bypasses were abandoned; one because the surgeon considered the vessels were 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 cases a graft was inserted and the operation was completed but in the opinion of the responsible consultant surgeon undertaking the procedure the bypass was not working at the end of the procedure. The immediate failure rate was, therefore, 5/195 (2.6%). Consequently, 193 (84%) patients randomised to bypass surgery underwent a completed surgical procedure as their first intervention, of which 188 were completed bypasses (Table 4).

In addition, four patients who had been randomised to balloon angioplasty underwent successful bypass surgery as their first intervention. By 12 months, 85/195 attempted bypass surgeries had resulted in clinical failure defined by death (n = 29), major amputation (n = 20) or a return or persistence of symptoms (rest pain, tissue loss) in the trial (operated) leg or the finding of a technical problem with the graft on surveillance (n = 36). Of the last group, 33 proceeded to have a second intervention, which in most cases was balloon angioplasty. A number of patients randomised to bypass surgery went on to have further interventions, amputation or to die within 12 months of randomisation as shown in Figure 3.

Patients randomised to balloon angioplasty: early (12-month) follow-up

Of the 224 patients randomised to balloon angioplasty, 216 underwent attempted balloon angioplasty (Figure 4).

In the opinion of the vascular interventional radiologist undertaking the procedure, 43 (20%) of these were immediate technical failures. In 10 cases this was because the vessel lumen could not be entered or the disease could not be completely crossed with a guide-wire. In 18 cases 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 patient could not tolerate the procedure. Two procedures were terminated because of vessel perforation after a guide-wire had been passed. One procedure was terminated immediately because the disease described as being present on preoperative duplex ultrasound was found not to be present at the time of angiography. In a further 10 cases there was immediate thrombosis of the balloon angioplasty channel and in six of those cases there was also distal embolisation that could not be rectified radiologically by means of either thrombolysis or aspiration. The anatomic extent and type of balloon angioplasty performed in the 203 patients undergoing attempted balloon angioplasty, and in whom a guide-wire was passed across at least part of the disease to be treated are shown in Table 5. In addition, 21 patients allocated to bypass surgery crossed over and underwent attempted balloon angioplasty as their first intervention; of these, five were immediate failures.

By 12 months, 109/216 (50%) attempted balloon angioplasties had resulted in clinical failure as defined by death (n = 21), amputation (n = 16) or a return or persistence of symptoms (rest pain, tissue loss) (n = 72) in the trial leg. Of these, 59 proceeded to have a second intervention, which in most cases was bypass surgery. A number of these patients went on to have further interventions, amputation or to die within 12 months of randomisation as shown in Figure 4.

Comparison of reinterventions following bypass surgery and balloon angioplasty

Following randomisation to, and attempted, bypass surgery, 109/195 (56%) patients were alive with the trial leg intact at 12 months without further intervention. This compares with 107/216 (50%) patients following randomisation to, and attempted, balloon angioplasty. Looking at the follow-up as a whole by intention to treat, bypass surgery was associated with a lower reintervention rate (41/224, 18.3%) than balloon angioplasty (59/228, 25.9%); a difference of 7.6% (95% CI 0.04% to 15.12%). When analysed by the first intervention received, the difference between reintervention following bypass surgery (33/199, 16.6%) and balloon angioplasty (67/237, 28.3%) was greater; a difference of 11.7% (95% CI 3.9% to 19.2%).

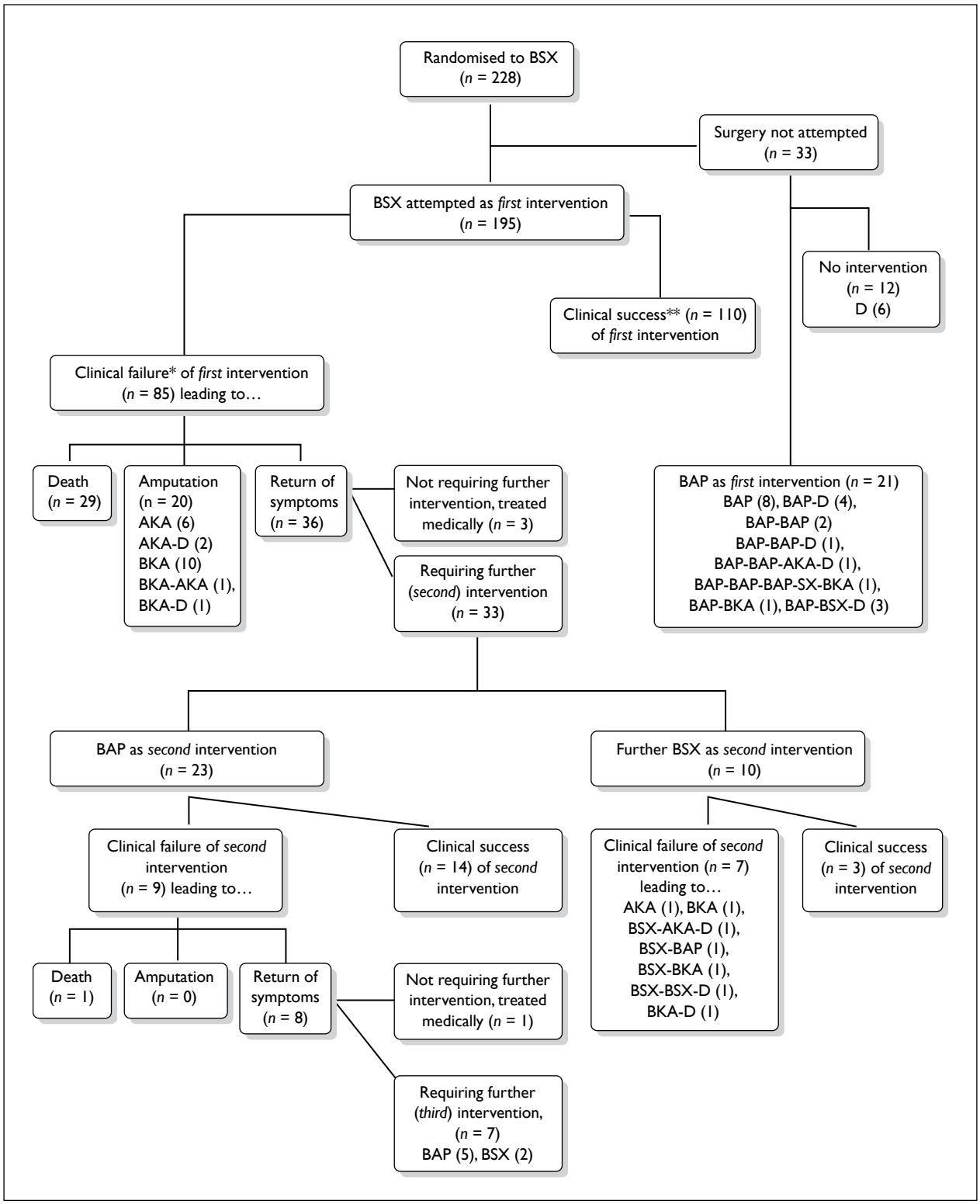


FIGURE 3 *CONSORT trial profile of patients randomised to bypass surgery (BSX): early (12-month) follow-up.*

**Clinical failure of an intervention is defined as death, amputation of trial leg, return or persistence of symptoms (rest pain/tissue loss), whether or not further intervention is required, by 12 months from randomisation. **Clinical success of an intervention is defined as patient alive with trial leg intact without further intervention at 12 months.*

Figures in italics describe all patient events (BAP, balloon angioplasty; BKA, below-knee amputation; AKA, above-knee amputation; D, death; NI, no intervention) during the first 12 months from randomisation in patients allocated to bypass surgery. A dash is used to separate the stages. So, for example, in the box entitled 'Clinical failure of second intervention (n = 7)' the phrase 'BSX-BSX-D (1)' means that one of those seven patients had further surgery (third intervention), then more surgery (fourth intervention), and then died.

TABLE 4 *Anatomic extent and type of bypass surgery*

	Prosthetic (ePTFE or Dacron) bypass	Ipsilateral LSV non-reversed vein bypass	Ipsilateral LSV reverse vein bypass	Non-ipsilateral LSV vein bypass	Composite (prosthetic and vein) bypass	Total
Femoral-AK-PA	23	5	30	0	4	62
Femoral-BK-PA	11	17	33	1	2	64
Femoral-CA	1	22	20	3	5	51
PA-CA	0	1	6	2	0	9
AK-to-BK-PA	0	0	1	0	0	1
IA-AKP	1	0	0	0	0	1
Total	36	45	90	6	11	188

AK, above knee; BK, below knee; CA, crural artery; ePTFE, Expanded PolyTetraFluoroEthylene; IA, iliac artery; LSV, long saphenous vein; PA, popliteal artery.
Four patients randomised to angioplasty crossed over to surgery: Fem-BKPA PTFE bypass graft; Fem-BKPA in situ vein graft; CIA-BKPA Dacron bypass graft; Fem-AKPA reverse vein graft.

Survival to primary end point (AFS) and secondary end point (ACM)

Figures 5 and 6 show Kaplan–Meier survival curves to the primary end point (AFS) and the secondary end point (ACM), also known as overall survival (OS).

Survival to the primary end point at 1 and 3 years was 68% and 57% for those randomised to a bypass-surgery-first strategy and 71% and 52% for those randomised to a balloon-angioplasty-first strategy. There were no significant differences in survival to either end point by randomised group. Hazard ratios (HRs) comparing randomised treatments by Cox proportional hazards are given in Table 6.

None of the planned comparisons provided strong evidence of a difference between the treatments. However, up to 6 months, there was a trend towards an increased hazard with bypass surgery relative to balloon angioplasty in terms of ACM, whereas after 6 months there was a trend towards a reduced hazard with bypass surgery in terms of AFS and ACM. A post-hoc analysis, carried out following examination of the survival curves, found a significantly reduced hazard in terms of AFS [adjusted HR 0.37 (95% CI 0.17 to 0.77), p = 0.008] and ACM [adjusted HR 0.34 (95% CI 0.17 to 0.71), p = 0.004] for bypass surgery relative to balloon 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 end point overall or in any of the time periods. The covariates with the strongest independent influence on survival to the end points were stratification group, diabetes, creatinine and age.

HRQoL results

At baseline the two treatment groups were balanced in terms of HRQoL. Patients in both treatment groups reported improved EQ-5D and SF-36 physical component summary scores by 3 months which were largely sustained during follow-up. However, little further improvement was observed beyond 3 months (Table 7). There was also improvement over a longer time period in the SF-36 mental component summary score. Although there is weak evidence that HRQoL may be somewhat better in the surgery group, there are no significant differences in HRQoL when the two treatment groups are compared. This finding is consistent across the three HRQoL scores.

Use of hospital resources

The use of hospital resources by the two groups on an intention-to-treat basis during the first 12 months from randomisation are compared in Table 8. There was no difference between the bypass-surgery-first and the balloon-angioplasty-first strategies in terms of the number of hospital admissions. However, patients randomised to bypass surgery spent significantly longer in hospital and required significantly more HDU and ITU care than those randomised to balloon angioplasty. Indeed, 23% of patients randomised to bypass

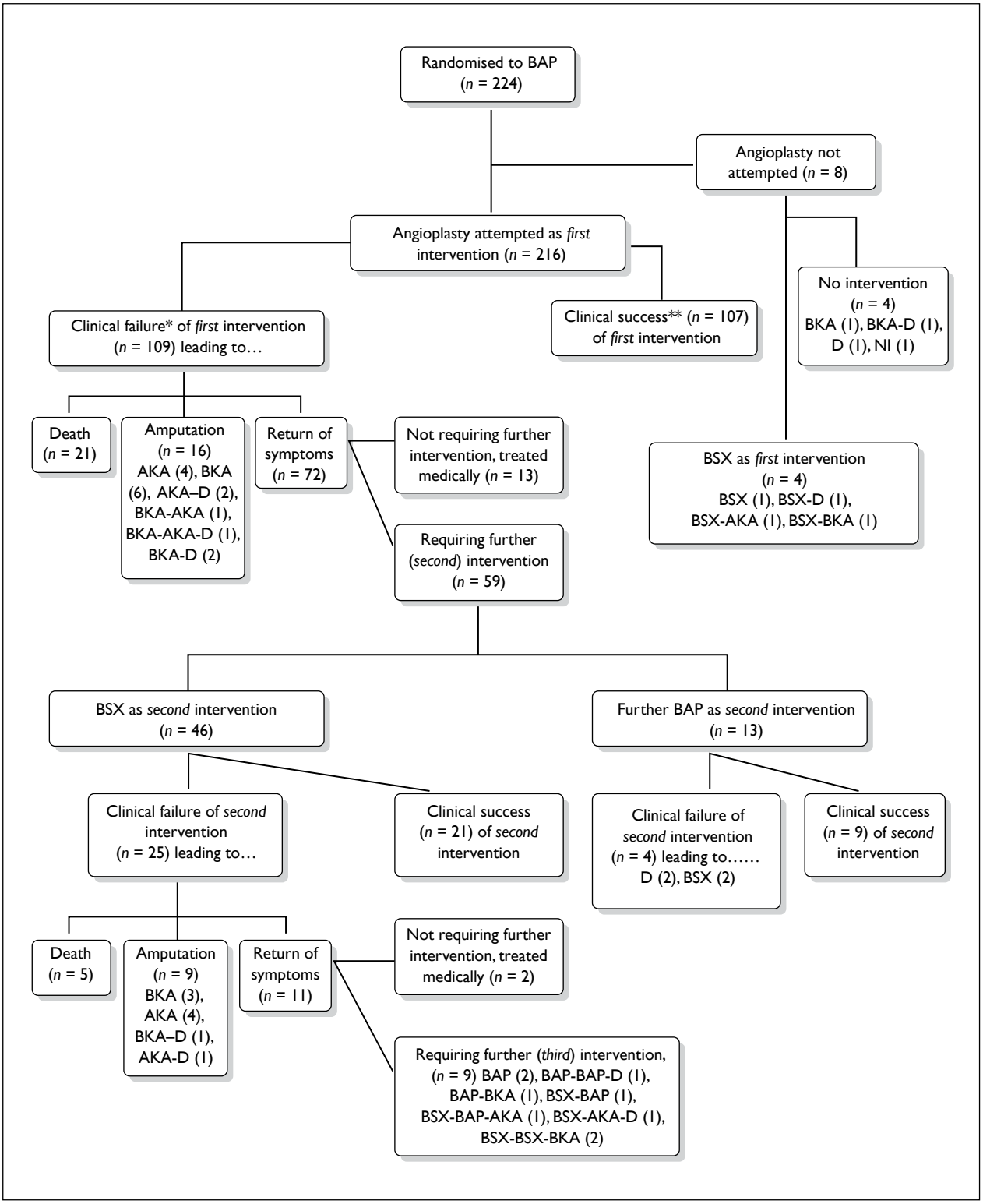


FIGURE 4 *CONSORT trial profile of patients randomised to balloon angioplasty (BAP): early (12-month) follow-up.*

**Clinical failure of an intervention is defined as death, amputation of trial leg, return or persistence of symptoms (rest pain/tissue loss), whether or not further intervention is required, by 12 months from randomisation. **Clinical success of an intervention is defined as patient alive with trial leg intact without further intervention at 12 months.*

Figures in italics describe all patient events (BSX, bypass surgery; BKA, below-knee amputation; AKA, above-knee amputation; D, death; NI, no intervention) during the first 12 months from randomisation in patients allocated to balloon angioplasty. A dash is used to separate the stages. So, for example, in the box entitled 'Requiring further (third) intervention (n = 9)', the term 'BSX-BSX-BKA (2)' means that of those who require a third intervention two patients had further surgery (third intervention), then more surgery (fourth intervention), then a BKA (fifth intervention). Then, because there is no '-D' at the end these two patients were alive at 12 months after randomisation.

TABLE 5 *Anatomic extent and type of balloon angioplasty*

Vessel(s) treated	Transluminal	Subintimal	Combined	Total
SFA only	22	31	4	57
PA only	8	9	2	19
CA only	2	2	0	4
SFA + PA	22	44	6	72
SFA + PA + CA	8	9	10	27
SFA + CA	3	1	3	7
PA + CA	8	5	3	16
PFA	1	0	0	1
Total	74	101	28	203

CA, crural artery (posterior tibial and/or anterior tibial and/or peroneal arteries); PA, popliteal artery; PFA, profunda femoris artery (deep femoral artery); SFA, superficial femoral artery.

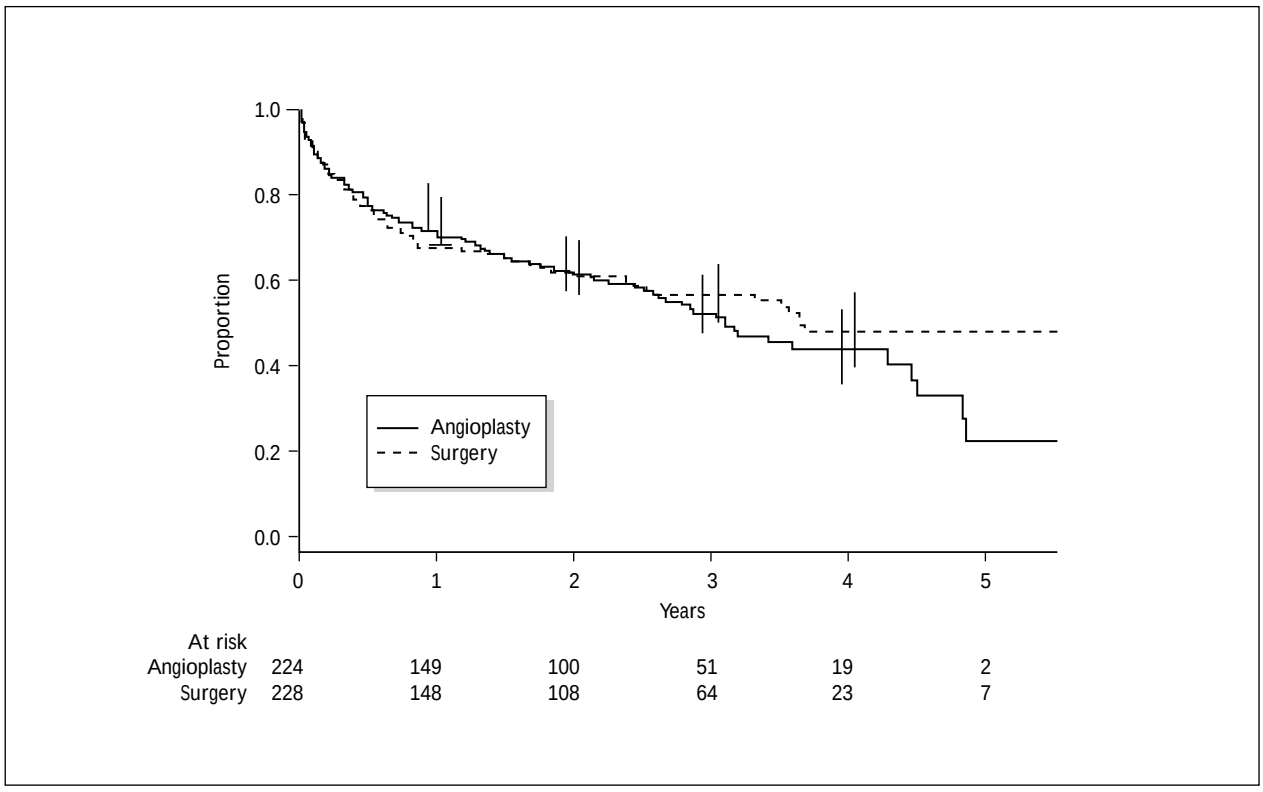


FIGURE 5 *Amputation-free survival following bypass surgery and balloon angioplasty by intention to treat (2005 analysis).*

surgery required HDU and 4% required ITU care during the first 12 months of follow-up compared with 0.5% and 7% of patients randomised to balloon angioplasty.

The mean cost of inpatient hospital treatment during the first 12 months of follow-up in patients randomised to a bypass-surgery-first strategy has been estimated as £23,656 (£20,431 hospital stay and £3225 procedure costs), which is approximately one-third higher than the £17,496 (£15,457 hospital stay and £2039 procedure costs) for patients randomised to a balloon-angioplasty-first strategy.

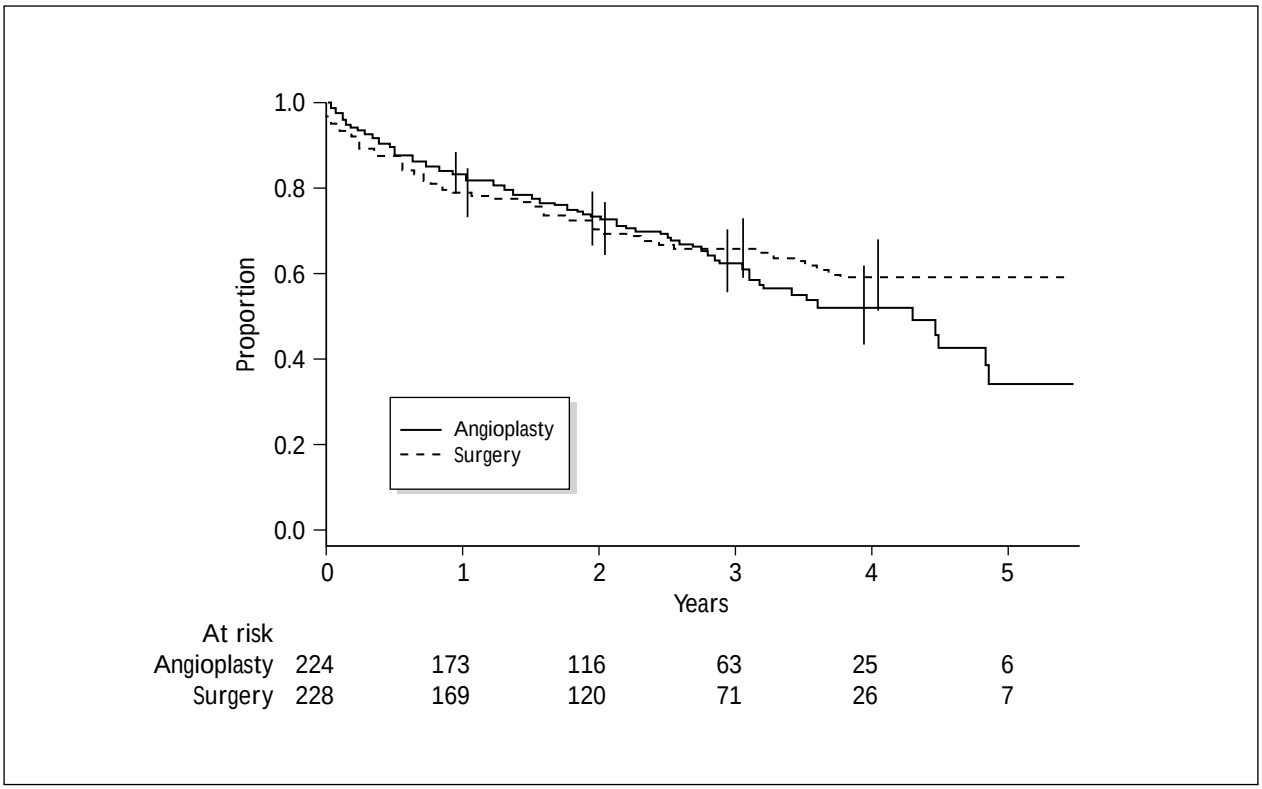


FIGURE 6 *All-cause mortality following bypass surgery and balloon angioplasty by intention to treat (2005 analysis).*

TABLE 6 *Comparison of hazard of amputation and/or death (amputation-free survival), and death (overall survival) for bypass surgery relative to balloon angioplasty*

	Number of events		Hazard ratio from Cox regression model (95% CI)	
Period	**Balloon angioplasty**	**Bypass surgery**	**Unadjusted**	**Adjusted[a]**
Amputation-free survival (primary end point)				
	n = 224	*n* = 228		
Whole follow-up period	106	98	0.89 (0.68 to 1.17)	0.88 (0.66 to 1.16)
Up to 6 months	46	50	1.07 (0.72 to 1.6)	1.04 (0.69 to 1.56)
After 6 months	60	48	0.75 (0.51 to 1.1)	0.73 (0.49 to 1.07)
After 2 years[b]	28	16	0.44 (0.22 to 0.88)	0.37 (0.17 to 0.77)
All-cause mortality (secondary end point)				
	n = 224	*n* = 228		
Whole follow-up period	87	79	0.90 (0.66 to 1.22)	0.95 (0.69 to 1.29)
Up to 6 months	26	31	1.20 (0.71 to 2.02)	1.27 (0.75 to 2.15)
After 6 months	61	48	0.78 (0.53 to 1.13)	0.81 (0.55 to 1.19)
After 2 years[b]	27	11	0.38 (0.19 to 0.77)	0.34 (0.17 to 0.71)

a Adjusted for age, sex, stratification group, body mass index, current or ex-smoker, creatinine, diabetes, statin use at baseline.
b Post-hoc analysis conducted after examination of the survival curves.

TABLE 7 *Comparison of HRQoL by intention to treat at different time points from randomisation*

	Balloon angioplasty (*n* = 224)	Bypass surgery (*n* = 228)	Crude difference, mean (SE)	Difference adjusted for baseline score, mean (SE, number of patients)	*p*-value
EQ-5D weighted index score					
Baseline	0.26 (0.32, 215)	0.29 (0.34, 206)	0.03 (0.03)	Ref.	
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
SF-36 physical component summary					
Baseline	17.50 (7.97, 213)	17.80 (9.06, 207)	0.30 (0.83)	Ref.	
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
SF-36 mental component summary					
Baseline	43.47 (11.64, 213)	45.17 (11.96, 207)	1.69 (1.15)	Ref.	
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 HRQoL.

Discussion and conclusions 1999–2005

The BASIL trial compares, for the first time within a multicentre RCT, the outcome of a 'bypass-surgery-first' with a 'balloon-angioplasty-first' revascularisation strategy in patients presenting with SLI caused by infrainguinal disease. The principal finding of the 2005 'interim analysis' is that in the medium term the outcomes following these two strategies were broadly similar in terms of AFS, ACM and HRQoL. However, when one examines the different patient outcomes in more detail and over different time periods following their first intervention, the relative advantages and disadvantages of each strategy become apparent.

In the short term, a bypass-surgery-first strategy is associated with significantly increased morbidity when compared with balloon angioplasty. Bypass surgery is also associated with a significantly greater length of stay in hospital, and use of HDU and ITU. This results in hospital costs over the 12 months after randomisation to bypass surgery being about a third higher than those after randomisation to balloon angioplasty. There is a particularly high incidence of cardiovascular, infective and wound complications following bypass surgery and a small but nonetheless clinically significant short-term reintervention rate for graft revision, thrombectomy and evacuation of haematoma. However, the 30-day mortality, which is not significantly higher than that observed following angioplasty, is low considering the severity of the disease and comorbidity exhibited by this cohort of patients. The 30-day technical failure rate is also low given the complexity of the surgery. In the longer term, after 2 years, bypass surgery appears to be associated with a significantly reduced risk of future amputation and/or death. In other words, if a patient is alive with their trial leg intact at 2 years after randomisation then, from that time onwards, they appear more likely to remain alive with their trial leg intact if they had originally been randomised to bypass surgery when compared with those randomised to balloon angioplasty. Although this result is highly statistically significant, one must be careful not to overinterpret this finding because it is the result of a post-hoc analysis, performed after the survival curves had been viewed, and the numbers of end points after 2 years is relatively small. Nevertheless,

TABLE 8 *Comparison of use of hospital resources by intention to treat during the first 12 months from randomisation*

Hospital resource usage	Patients randomised to balloon angioplasty (*n* = 224)				Patients randomised to bypass surgery (*n* = 228)				*p*-value[a]
	Mean	SD	Min	Max	Mean	SD	Min	Max	
Number of admissions to hospital	2.06	1.50	0	10	2.14	1.30	1	8	0.286
Total days spent in hospital	36.22	51.37	0	334	46.76	53.86	0	366	< 0.001
Days spent in ITU	0.04	0.60	0	9	0.13	0.94	0	12	0.012
Days spent in HDU	0.18	1.17	0	16	0.65	1.60	0	11	< 0.0001
Number of bypass procedures	0.26	0.52	0	3	0.95	0.50	0	4	
Number of angioplasty procedures	1.05	0.36	0	3	0.25	0.54	0	3	

a Wilcoxon two-sample test.

it raises the intriguing possibility that, despite the increased short-term morbidity, patients may enjoy a more durable benefit from a bypass-surgery-first strategy than a balloon-angioplasty-first strategy (see Chapter 3).

Balloon angioplasty is associated with a much higher immediate failure and 12-month reintervention rate than bypass surgery. Further analysis of the clinical data and pre-BAP angioplasty imaging may help to identify those patients and lesions that respond poorly to balloon angioplasty and would be better treated by bypass surgery (see Chapter 4). Overall, approximately half of the attempted balloon angioplasties failed within the first 12 months and over half of these patients went on to have bypass surgery as a second procedure. The clinical failure rate of surgery over the first 12 months is much lower. Furthermore, although some patients randomised to bypass surgery went on to have balloon angioplasty as a secondary procedure, in many cases this appears to have been to treat vein graft stenoses detected in the course of surveillance. Consequently, the rate of reintervention and magnitude of the reintervention during the first 12 months were significantly higher in the balloon-angioplasty-first group. However, the morbidity associated with BAP was low, the hospital stay was short (and so the costs were low) and there was no suggestion at this stage that a 'failed' balloon angioplasty prejudiced the results of any subsequent bypass surgery that was deemed necessary and appropriate (but see Chapter 5). Unfortunately, a sizeable minority of patients in both groups underwent repeated procedures only to eventually die and/or lose their leg within the first 12 months. This suggests that some patients would probably have been better served by primary amputation rather than by attempts, either by bypass surgery or balloon angioplasty, at revascularisation.

Not surprisingly, the data indicated that the patients in this trial had a very low HRQoL before treatment. There was no significant difference in HRQoL between the two strategies. This suggests perhaps 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 HRQoL. The short-term improvements in perceptions of physical and mental well-being were sustained but neither treatment led to continuing improvement in HRQoL beyond the first few months. This may be because patients with SLI are generally elderly and socially disadvantaged with multiple comorbidities (see Chapter 7).

The hospital costs over the first year are approximately a third higher with a bypass-surgery-first than with a balloon-angioplasty-first strategy. Although the cost of the surgical procedure is greater than that of balloon angioplasty, the main difference is related to the length of hospital stay and, in particular, the much greater requirement for patients undergoing bypass surgery to be cared for within an HDU or ITU environment. No attempt was made to quantify the use, and associated costs, of health and social services outside hospital. However, this is likely to represent

a significant additional financial burden in certain patients, especially those who ultimately require amputation (see Chapter 7).

Although not primarily the subject of the trial, it is worth noting how few patients were on antiplatelet agents and statin therapy, and how many patients were still smoking, upon entry to the trial. The reasons for this are unclear and probably multi-factorial. However, this is an observation that has been made and specifically commented upon in other recent studies looking at similar groups of patients.[49] There is clear evidence that so-called best medical therapy comprising antiplatelet agents, 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 significant reduction in the risk of future cardiovascular events, including the requirement for limb-salvage intervention and amputation.[3] One can only speculate as to how many of the BASIL trial patients, had they been receiving best medical therapy, would have avoided developing SLI and its consequences. It is also possible that a more aggressive implementation of best medical therapy would have improved the results of the trial interventions. Improving the medical management of patients with, and at risk of developing, SLI would seem to be an urgent priority in primary and secondary care.

The BASIL trial clearly indicates that, almost regardless of what treatment is received, many patients with SLI have an extremely poor prognosis in terms of major limb amputation, death and HRQoL. Furthermore, the audit delivers the new and perhaps unexpected finding that up to half of all patients presenting with SLI to major UK vascular units and undergoing diagnostic imaging are not considered for immediate/early revascularisation, whether that be by bypass surgery or balloon angioplasty. Although not the subject of this trial and audit, there is a further group of patients who present with SLI but are not offered diagnostic imaging because their disease is too advanced and/or their medical condition is too poor. Patients who actually undergo revascularisation for SLI, by either bypass surgery or balloon angioplasty, therefore appear to represent the tip of an iceberg, the true dimensions of which remain incompletely defined. This means that any RCT of interventions for SLI, including the BASIL trial, will be limited in its generalisability to the entire population of patients presenting with SLI, many of whom are actually treated conservatively or by primary amputation (discussed further in Chapter 10). However, the BASIL audit indicates that approximately one-third of patients presenting with SLI and who undergo diagnostic imaging, and who are considered to be candidates for revascularisation, fell into the trial's grey area of equipoise; and over two-thirds of these were randomised. The results of the BASIL trial are applicable and generalisable to very large numbers of patients presenting to vascular units with SLI and undergoing attempted revascularisation around the world.

In summary, SLI imposes a very significant human cost as well as a major economic burden upon health- and social-care resources not only in developed, but also in an increasing number of developing, countries. It is hoped 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, for the first time, upon level 1 evidence regarding the relative risks and benefits of a bypass-surgery-first and a balloon-angioplasty-first strategy. The medium-term results of the BASIL trial indicate that patients presenting with SLI caused by infrainguinal atherosclerosis and who appear technically suitable for both bypass surgery and balloon angioplasty can reasonably be treated with either modality in the first instance, depending on individual patient characteristics and local expertise. However, notwithstanding the high failure and reintervention rate associated with balloon angioplasty, patients who are expected to live for less than 1 to 2 years and have significant comorbidity should probably, where possible, be offered balloon angioplasty first (see Chapter 4). Even if the procedure fails, the patient may be able to go on to have bypass surgery if considered appropriate (but see Chapter 5). Angioplasty also appears to be a much less expensive option, at least in the short term. By contrast, in patients expected to live for more than 2 years and who are relatively fit, the apparent superior durability of, and reduced reintervention rate associated with, surgery may well outweigh the short-term considerations of increased morbidity and cost. Longer-term follow-up and a more detailed analysis of the BASIL trial data set are likely to allow these provisional recommendations to be refined in the future (see Chapter 3).

The strengths and weaknesses of the BASIL trial are further discussed in Chapter 10.

Chapter 3

The 2008 'final' main end points analysis

Background 2005–8

As described in Chapter 2, an 'interim' analysis reported in the Lancet in 2005[50] indicated that short-term clinical outcomes following bypass surgery and balloon angioplasty for SLI were similar but that over the first 12 months surgery was approximately one-third more expensive. However, there was a suggestion that after 2 years from intervention patients would be more likely to remain alive and without amputation if they had been originally randomised to surgery. Although this result was statistically significant, it was based on a post-hoc analysis performed after the survival curves had been viewed, and the numbers of end points after 2 years was relatively small. In order to determine whether this apparent advantage of surgery is real and maintained in the longer term, patients were followed for a further 2½ years.

Methods 2005–8

The BASIL trial methods have been described in detail in Chapter 2.

Angiograms were scored according to the Bollinger method (infrainguinal segments) and the Trans-Atlantic Society Consensus (TASC) II criteria.[51,52]

We measured self-reported HRQoL using the Vascular Quality of Life Questionnaire (VascuQoL), the EuroQoL 5D (EQ-5D) and the SF-36 (Short Form 36).[42,53] The VascuQoL is a disease-specific questionnaire designed to assess specific elements of HRQoL for individuals with lower limb ischaemia. It includes 25 items (questions) in five domains: pain, symptoms, life activities, social and emotional. Each question has a seven-point response scale ranging from 1 (worst possible HRQoL) to 7 (best possible HRQoL). Responses are averaged for individual domain and composite total scores. The EQ-5D responses were converted into a single weighted utility (preference-based) score using the original time trade-off tariff set.[44] For VascuQoL and EQ-5D, higher scores indicate better health and well-being as perceived by the patient. These measures were collected at baseline and at 3, 6, 12, 24 and 36 months after randomisation. We conducted analyses using complete data (case-wise deletion of observations when HRQoL scores were missing)

Following randomisation, we obtained data on all subsequent interventions and on hospital stays and day cases during follow-up. Patient-specific hospital use was measured using the duration of hospital stay as an aggregate unit of services provided. Total length of hospital stay was measured for 3 years from the date of randomisation. Hospital use was valued using the average specialty-specific cost per day using the Scottish system of hospital cost statistics.[54] All procedures (surgical, radiological and amputations) were measured using patient-specific reported anaesthetic, theatre and recovery-suite times and valued using national pay scales for staff and prices for materials. Hospital stay and procedure costs are reported on a price base of the financial year 2006–7 and discounted at 3.5%. Further information on health economic methods and analysis can be found in Chapter 7.

Statistical analysis

The power to detect an HR of 0.5 for bypass surgery versus balloon angioplasty from new events (amputation, death) after 2 years from randomisation was estimated at 90% with $p = 0.05$. This was based on a simulation study using a Weibull parametric survival model using separate hazards before and after 2 years from randomisation. As the expected direction of difference was known, a one-sided test was specified and agreed by the funding body (HTA). However, the decision to use a one-sided test has been questioned by the reviewers. We respectfully suggest that the decision to use a one-sided or two-sided test depends on the action that would be taken in response to a finding. The purpose of a significance level is to control the level of false positives. A one-sided test should only be carried out if it would be certain that, had the results gone in the other direction, no matter how strongly, they would not be interpreted as anything other than chance. In planning the protocol for further follow-up we, and the funding body (HTA), felt that this would apply here.

The second (2008) statistical analysis was conducted according to a prespecified protocol

that was finalised before the further follow-up data (2005–8) were available (see full statistical plan in Appendix 2).

A Cox proportional hazards model was used to examine survival to the primary (AFS) and secondary (OS) end points. For the survival analyses, patients with no report of death were taken as censored at the end of February 2007 if their death information was from ISD, as censored at the end of July 2007 if their death information was from the Office for National Statistics (ONS), or at the date of last clinical contact if it was after this date. In addition, four patients who were lost to follow-up and who were thought unlikely to have their deaths recorded in the UK were censored at their last follow-up times; all within 1 year and 1 month of randomisation. An analysis was undertaken to evaluate new information from the additional follow-up since the 2005 analysis, highlighting the period 2 years beyond randomisation. The protocol stated that 'If this additional data, by itself, provides evidence of a higher event rate for those assigned to bypass (one-sided test) then it will be strong evidence that the previously identified trend was not due to chance.'

The reviewers have suggested that using updated values of covariates at 2 years post-randomisation might have given a more complete adjustment for the non-randomised comparison between surgery and angioplasty. It is further suggested that one would clearly expect (1) the baseline covariates to be less predictive 2 years on and (2) potentially substantial differences not just in the baseline covariates of those left at 2 years but even more so in the updated values – hence leading to a better adjustment of the treatment effect. However, we did not feel it was appropriate to adjust for post-randomisation covariates as they could have been affected by treatments, and hence could give a biased result that would be difficult to interpret. For example, were we to use some measure of fitness at 2 years (e.g. ankle pressures) it might have been the effect of one treatment on this that had the result of improving survival. However, if we were wrongly to adjust for this the real benefit of this treatment would not be apparent.

For the HRQoL analysis descriptive statistics were based on completed baseline and follow-up questionnaires with no missing items. VascuQoL and EQ-5D weighted scores were assessed using simple linear regressions. Adjusted differences allowing for baseline scores were based on bias-corrected matching estimators.[46] The full sample method was used to summarise the cumulative distribution of hospital costs arising from the time of randomisation to follow-up (3 years) using arithmetic mean costs observed for all patients. Confidence intervals for estimated untransformed arithmetic mean costs were estimated analytically and empirically using bootstrapping techniques to check for the adequacy of the assumptions made regarding the normality of the cost distributions.[55] We found that standard t tests and t test-based confidence intervals were very similar to those based on the bootstrap.

Results 2005–8

CONSORT diagrams for the trial are presented below and in Chapter 2. The baseline characteristics of the patients randomised into each group (228 to bypass surgery, 224 to balloon angioplasty) were similar and have also been previously reported in Chapter 2.[50] As is typical of patients presenting with SLI, many were elderly, over 40% were diabetic, over a third were still smoking, most had a significant cardiovascular past medical history, and a quarter had SLI affecting both legs. In terms of disease severity in the trial leg, 93 had rest pain only and an ankle pressure ≥ 50 mmHg; 23 had rest pain only and an ankle pressure < 50 mmHg; 222 had tissue loss and an ankle pressure ≥ 50 mmHg; and 114 had tissue loss and an ankle pressure < 50 mmHg. As a consequence, 74% of patients had tissue loss (ulceration, gangrene) and 30% had ankle pressures < 50mmHg so fulfilling the European Consensus criteria for critical limb ischaemia (CLI). With respect to TASC II classification of disease extent and severity, in 39 patients (21 randomised to bypass and 18 randomised to angioplasty) angiograms were of insufficient quality to permit classification. Of the remainder, 12 were type A (least severe), 122 were type B, 186 were type C and 93 were type D (most severe). This distribution was very similar in the two randomised groups.

Apart from four patients lost to follow-up, there was a minimum of 3 years' complete follow-up for all patients with 54% of patients being followed for more than 5 years; the longest follow-up was just over 7 years. The status of the patients at the end of follow-up is shown in Table 9.

Procedures undertaken up to 3 years are shown in the CONSORT diagram (Figure 7).

TABLE 9 *Patient status at final follow-up*

	All (*n* = 452)		**Balloon angioplasty (*n* = 224)**		**Bypass surgery (*n* = 228)**	
	n	**%**	***n***	**%**	***n***	**%**
Lost to follow-up	4		1		3	
In follow-up or dead	448	100%	223	100%	225	100%
Status						
Dead	250	56%	131	59%	119	53%
Alive with amputation	30	7%	10	4%	20	9%
Alive no amputation	168	38%	82	37%	86	38%

Looking first at the follow-up period as a whole, surgery was associated with a non-significant increase in restricted mean survival[56] of about 3 months for both AFS (surgery 3.84 years, angioplasty 3.62 years, difference 0.22 years, 95% CI −0.34 to 0.78) and OS (surgery 4.48 years, angioplasty 4.25 years, difference 0.23 years, 95% CI −0.33 to 0.79) when compared with angioplasty. However, as had been anticipated from the interim analysis, in the time-dependent Cox proportional hazards analysis prespecified in the statistical plan, the relative hazards of amputation and death following bypass surgery and balloon angioplasty were found to change significantly over time. Specifically, whereas out to 2 years from randomisation the hazards were slightly (non-significantly) higher for bypass surgery, beyond 2 years those patients initially randomised to surgery had a significantly reduced hazard for overall mortality (Table 10).

Although there was also a trend towards better amputation-free survival in the surgery group after 2 years this was not statistically significant.

These findings are shown in the survival curves (Figures 8 and 9).

In order to examine the strength of the new evidence collected since February 2005, as specified in the protocol, we carried out a person-years analysis of events that occurred after 2 years from randomisation. This showed that the trend to improved AFS after 2 years seen after randomisation to surgery in the earlier preliminary (2005) analysis was not continued (Table 11). The

TABLE 10 *Cox proportional hazards analysis, by time from randomisation < 2 years and > 2 years*

End point	**Time from randomisation**	**Estimate**	**95% CI**	***p*-value (two-sided)**
Amputation-free survival				
Unadjusted	Before 2 years	1.05	(0.78 to 1.41)	0.76
	After 2 years	0.80	(0.55 to 1.16)	0.24
Adjusted[a]	Before 2 years	1.03	(0.76 to 1.39)	0.85
	After 2 years	0.85	(0.50 to 1.07)	0.11
Overall survival				
Unadjusted	Before 2 years	1.17	(0.83 to 1.65)	0.36
	After 2 years	0.62	(0.43 to 0.90)	0.01
Adjusted[a]	Before 2 years	1.19	(0.84 to 1.68)	0.32
	After 2 years	0.61	(0.50 to 0.75)	0.009

a Adjusted for stratification, creatinine, body mass index, diabetes, age, smoking, statin at baseline and below-knee Bollinger angiogram score.

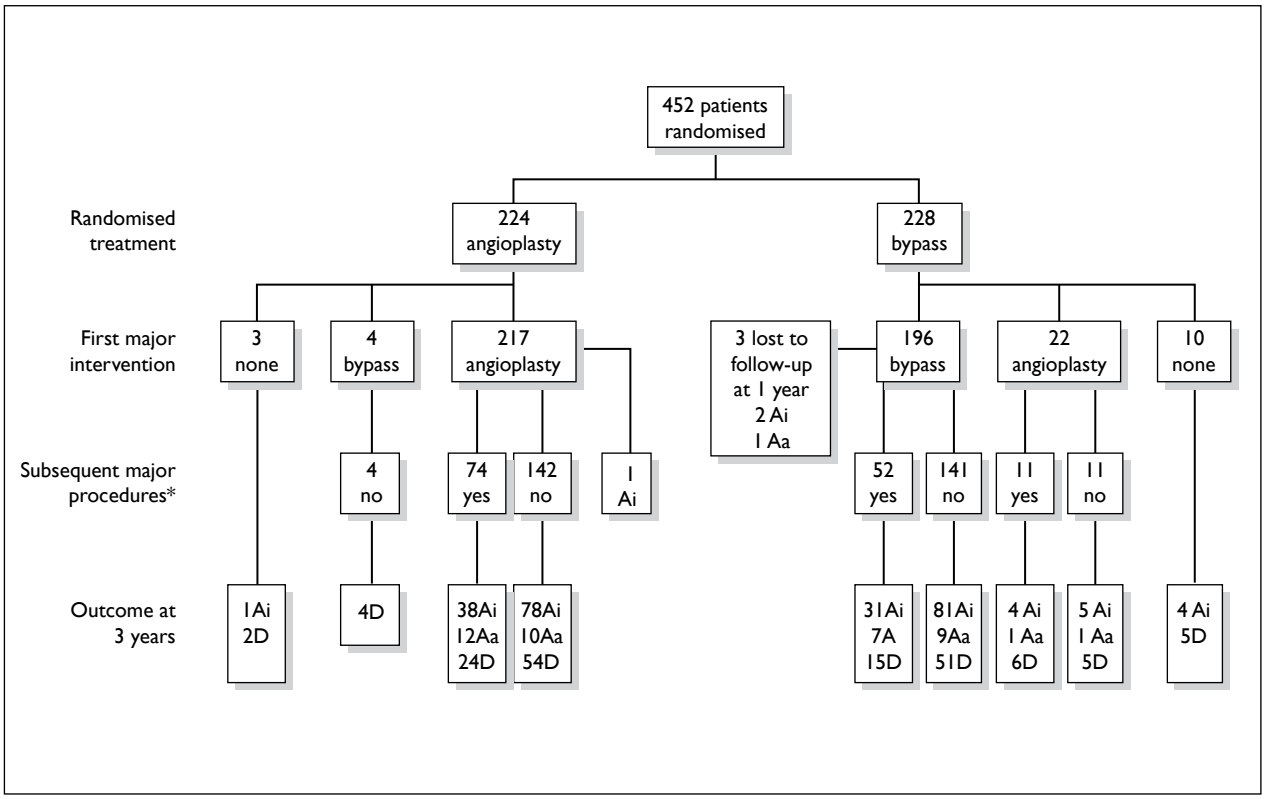


FIGURE 7 *CONSORT diagram showing patient journeys and interventions up to 3 years. Ai, alive with trial leg intact; Aa, alive with trial leg amputated; D, dead.*

**Major procedures: balloon angioplasty, stent, thrombolysis, bypass, surgical angioplasty, endarterectomy and vein patch, thrombectomy, profundaplasty.*

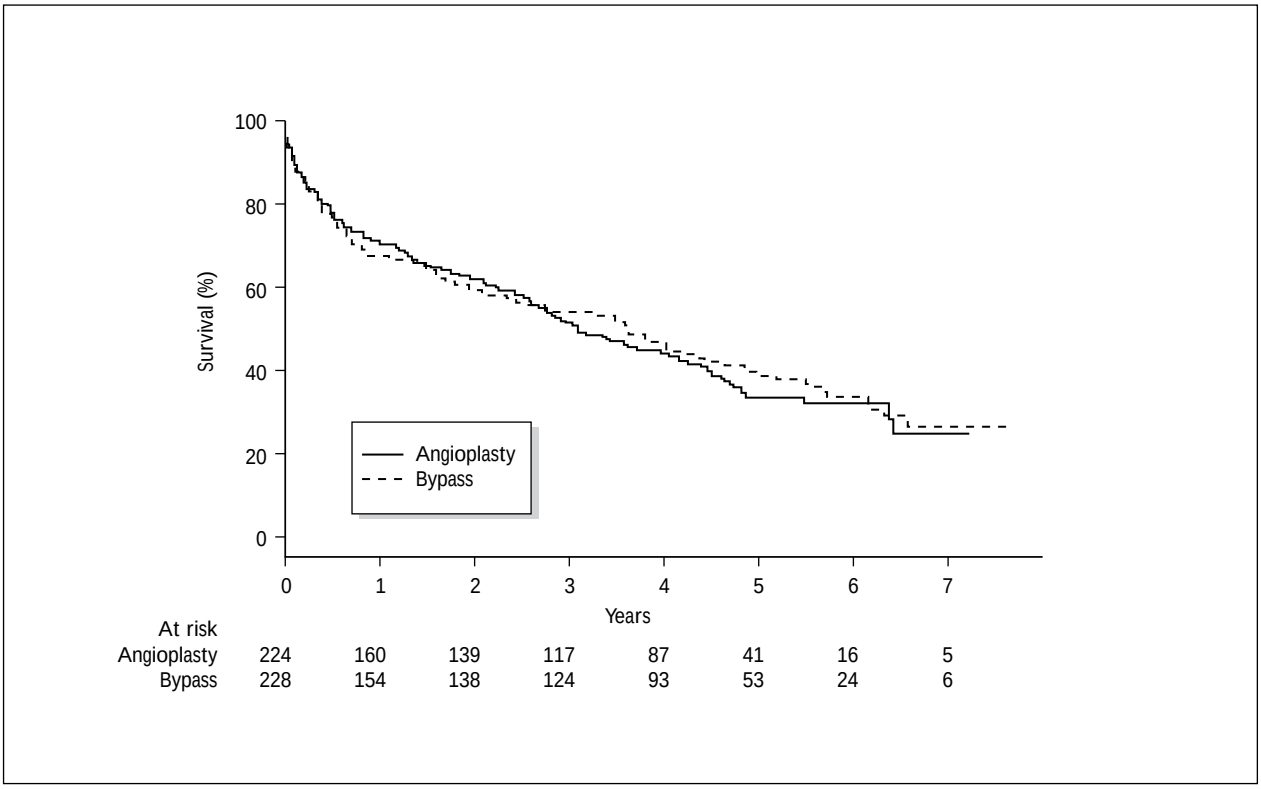


FIGURE 8 *Survival to primary end point of major amputation of trial leg, or death (2008 analysis).*

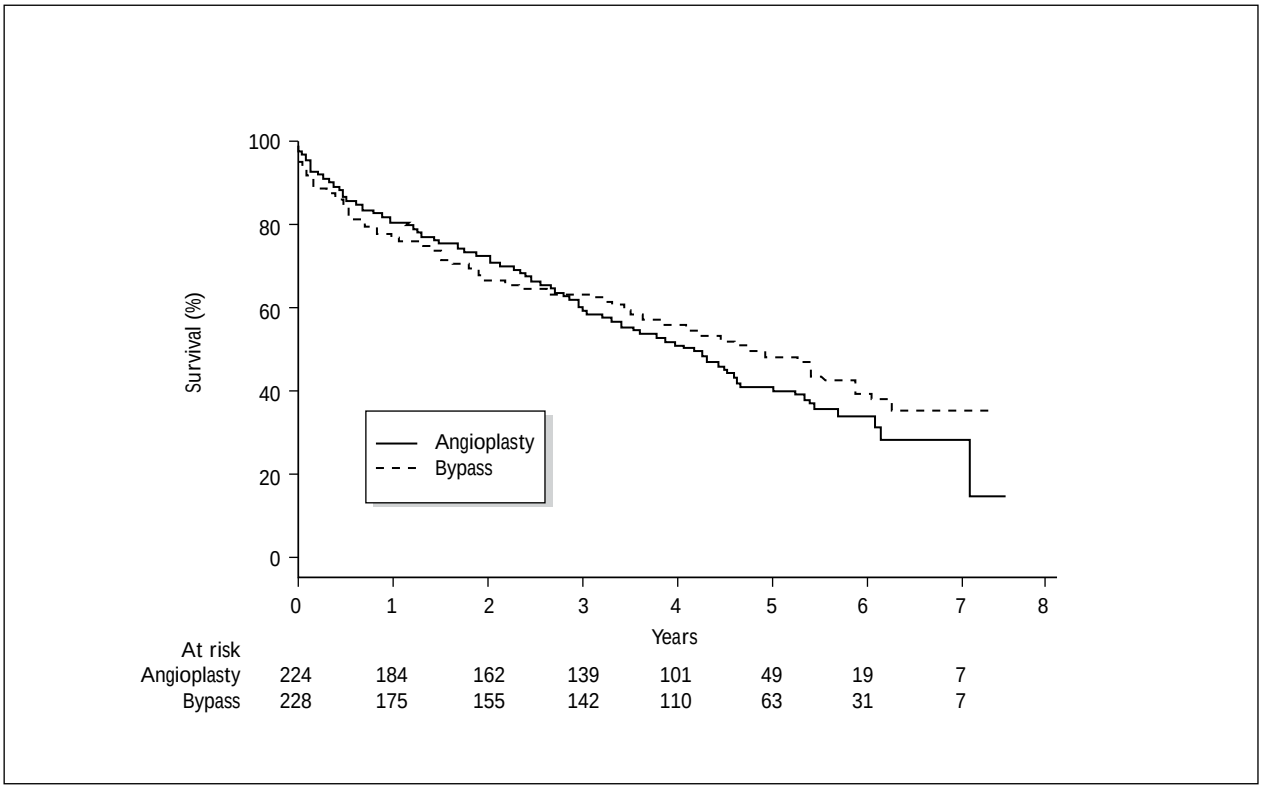


FIGURE 9 *Survival to death by randomised treatment (2008 analysis).*

TABLE 11 *Events and years of follow-up divided by time before and after 2 years from randomisation and by events that occurred before and after February 2005 when data for the initial analyses were censored*

		Balloon angioplasty			Bypass surgery				
		Years of follow-up	Events	Rate per year	Years of follow-up	Events	Rate per year	Rate ratio	*p*-value[a]
All follow-up time									
Deaths	To 2 years	370.91	61	0.1645	359.96	70	0.1945	1.18	0.852
	After 2 years	394.25	70	0.1776	431.09	49	0.1137	0.64	**0.010**
PEPs									
	To 2 years	328.73	84	0.2555	325.18	88	0.2706	1.06	0.670
	After 2 years	334.03	57	0.1706	370.83	51	0.1375	0.81	0.152
To February 2005									
Deaths	To 2 years	344.39	57	0.1655	337.51	67	0.1985	1.20	0.864
	After 2 years	142.78	26	0.1821	151.51	13	0.0858	0.47	**0.017**
PEPs	To 2 years	304.72	81	0.2658	305.97	84	0.2745	1.03	0.612
	After 2 years	115.72	22	0.1901	135.79	15	0.1105	0.58	**0.070**
After February 2005									
Deaths	To 2 years	26.52	4	0.1508	22.44	3	0.1337	0.89	0.590
	After 2 years	251.47	44	0.1750	279.59	36	0.1288	0.74	0.104
PEPs	To 2 years	24.01	3	0.1250	19.20	4	0.2083	1.67	0.854
	After 2 years	218.30	35	0.1603	235.04	36	0.1532	0.96	0.470

PEP, primary end point (amputation-free survival).
a One-sided *p*-value from exact conditional test based on the binomial distribution.

rate ratio in the later period was close to 1.0 and the evidence for a reduced hazard in the surgery group was no longer significant when all the data were combined. This was because relatively more amputations occurred after 2 years in those who had been assigned to surgery. By contrast, the trend to significantly fewer deaths in those randomised to surgery did continue, to some extent. However, the rate ratio was less extreme in the recently collected data (0.74 compared with 0.64) and the one-sided p-value for the data collected since February 2005 was only significant at p = 0.104. Hence, following the protocol, we have not found strong evidence that the reduced hazard due to surgery after 2 years is more than a chance effect. Taking the whole follow-up period, however, there was a reduced hazard for those randomised to surgery in the period after 2 years from randomisation, in agreement with the results of the Cox proportional hazards analysis.

Conditional survival curves calculated for those patients who survived to 2 years after intervention show that initial randomisation to surgery is associated with a significant improvement in subsequent restricted mean OS of 7.3 months (95% CI 1.2 months to 13.4 months; p = 0.02) and a non-significant increase in restricted mean AFS of 5.9 months (95% CI –0.2 months to 12.0 months; p = 0.06). The advantages of surgery for survival from randomisation were smaller and there was no statistically significant difference in restricted mean life for mortality [2.8 months longer for randomisation to surgery (95% CI –4.1 months to 9.7 months; p = 0.42)] and for time to primary end point [2.6 months longer (95% CI –4.2 months to 9.5 months; p = 0.44)].

There was no evidence for differential effectiveness by any of the interactions prespecified in the statistical protocol; namely, Bollinger angiography scores, TASC II classification, stratification group at randomisation, and a predictive score based on a combination of all baseline covariates. This lack of differential effectiveness was present for the follow-up period as a whole, as well as when the periods before and after 2 years from randomisation were analysed separately. No other interactions, outwith those prespecified, were examined.

Patients in both treatment groups reported improved VascuQoL and EQ-5D scores by 3 months (Table 12), but little additional improvement was recorded beyond 3 months. The disease-specific VascuQoL scales provide further strong evidence that both angioplasty and surgery have a significant positive short run impact on all domains affected by SLI that is largely maintained while amputation is avoided. The improvement in HRQoL was non-significantly better in the surgery group. However, crude and adjusted differences are very similar and not significantly different from zero at all time intervals up to 36 months. Patients in both treatment groups reported virtually identical levels and trajectories in the disease-specific VascuQoL and EQ-5D preference-based measures.

Over the first year from randomisation the mean cost of inpatient hospital treatment in patients randomised to surgery was estimated at £22,002 (£18,369 hospital stay and £3635 procedure costs), which is approximately a third higher than the £16,582 (£14,468 hospital stay and £2115 procedure costs) for patients randomised to angioplasty (Table 13). This difference in mean total hospital and procedure costs of around £5420 was significant (95% CI £1646 to £9195) at 1 year. However, because of the increased costs incurred by the angioplasty patients in years 2 and 3, this difference decreased to £3533 (£29,006 surgery versus £25,472 angioplasty) and was no longer significant by the end of year 3.

Discussion and conclusions 2005–8

A preliminary analysis of the BASIL trial reported in 2005 (see Chapter 2) suggested that short-term clinical outcomes from bypass surgery and angioplasty were similar but that, as well as being more morbid, surgery was approximately one-third more expensive over the first 12 months.[50] However, there was also a suggestion that, after 2 years from intervention, patients would be more likely to remain alive and without major limb amputation if they had been originally randomised to surgery. Although this difference was statistically significant, because of limited long-term follow-up, and the fact that this finding was based on a post-hoc analysis of a relatively small number of late events, the statistical advice was to exercise caution and to consider this an interim finding in need of further testing.

In order to confirm or refute this apparent long-term advantage for surgery, further funding was obtained from the HTA to allow trial patients to be followed for a further 2½ years. This additional follow-up period was chosen on the basis of a careful statistical power calculation (see Appendix

TABLE 12 *Comparison of VascuQoL and EQ-5D by intention-to-treat analysis at different time points from randomisation*

	Angioplasty (*n* = 224)	Surgery (*n* = 228)	Crude difference, mean (SE)	Adjusted difference for baseline score, mean (SE, number of patients)	*p*-value
VascuQoL					
Baseline	2.78 (1.01, 215)	2.91 (1.10, 207)	0.13 (0.10)	1	
0–3 months	4.32 (1.39, 162)	4.55 (1.30, 153)	0.23 (0.15)	0.17 (0.14, 306)	0.22
3–6 months	4.28 (1.38, 143)	4.54 (1.34, 131)	0.26 (0.16)	0.19 (0.15, 268)	0.20
6–12 months	4.53 (1.42, 133)	4.67 (1.37, 121)	0.14 (0.18)	0.02 (0.17, 248)	0.91
12–24 months	4.58 (1.53, 62)	4.72 (1.50, 78)	0.14 (0.25)	0.14 (0.28, 134)	0.63
24–36 months	4.61 (1.41, 46)	4.44 (1.55, 49)	0.17 (0.30)	–0.39 (0.30, 92)	0.20
EQ-5D 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
12–24 months	0.56 (0.32, 63)	0.59 (0.34, 76)	0.03 (0.06)	0.08 (0.06, 132)	0.16
24–36 months	0.61 (0.25, 48)	0.54 (0.35, 49)	0.07 (0.06)	–0.06 (0.05, 93)	0.29

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

2) based on observed and anticipated events rates. This final analysis of the BASIL trial has now been conducted according to the prespecified statistical plan that was agreed before the additional follow-up data became available (see Appendix 2).

An intention-to-treat analysis of these long-term follow-up data has shown that those patients who survive 2 years and who were initially randomised to surgery gain a significant c. 7 months of additional life (95% CI 1 month to 13 months) and an additional non-significant c. 6 months of amputation-free life (95% CI 0 months to 12 months) over the subsequent follow-up from 2 years to 7 years 9 months from randomisation. These further data lend considerable support to the earlier findings but true confirmation would need a separate, independent data set. To the authors' knowledge, however, no other trial comparable to BASIL is under way at the present time so such a data set may never become available.

One possible explanation for the finding of better late survival for patients randomised to surgery might be the survival of the fitter patients, who may do better with surgery, into the second period. However, the fact that the observed differences in OS in the period beyond 2 years were not attenuated by adjustment for covariates found to be predictive of outcome at baseline makes this explanation very unlikely (see also Chapter 4).

Patients in both treatment groups reported improved generic and disease-specific HRQoL scores by 3 months but little further change was recorded thereafter. These data provide further evidence that both angioplasty and surgery have a positive short-run impact on all HRQoL domains affected by SLI. As in the earlier analysis to 12 months, there is no significant difference in HRQoL between the two treatment groups out to 3 years (see Chapter 7).

The preliminary (2005) analysis suggested that surgery was approximately one-third more expensive than angioplasty over the first 12 months. These statistically significant additional short-term (12-month) costs of about £5500 are supported by the present further analysis and comprise both increased hospital stay (c. £4000) and procedure (c. £1500) costs. However, because of the increased costs incurred by the angioplasty patients in years 2 and 3, largely as a result of increased hospital admissions, this difference decreases to about £3500 by 3 years and is no longer significant. Chapter 7 gives a

TABLE 13 *Mean costs (£) and cost differences (95% CI) over 3 years follow-up*

	Angioplasty (*n* = 223) (£)	**Surgery (*n* = 225) (£)**	**Mean cost difference[a] (£)**
Year 1			
Hospital stay	14,468	18,369	3902
	(11,755 to 17,179)	(15,802 to 20,935)	(104 to 7700)
Procedure cost	2115	3635	1519
	(1831 to 4398)	(3334 to 3933)	(1120 to 1917)
Total cost	16,582	22,002	5420
	(13,755 to 19,409)	(19,337 to 24,667)	(1646 to 9195)
Years 2–3			
Hospital stay	8597	6484	–2113
	(6185 to 11,008)	(4732 to 8235)	(–5157 to 931)
Procedure cost	294	520	226
	(184 to 403)	(336 to 704)	(12 to 439)
Total cost	8890	7003	–1887
	(6449 to 11,332)	(5196 to 8810)	(–4919 to 1145)
Years 1–3			
Hospital stay	23,064	24,852	1789
	(18,893 to 27,234)	(21,591 to 28,114)	(–3537 to 7114)
Procedure cost	2409	4153	1744
	(2102 to 2716)	(3785 to 4522)	(1257 to 2231)
Total cost	25,472	29,006	3533
	(21,190 to 29,755)	(25,647 to 32,365)	(–1857 to 8923)

UK£ 2006–7 pay and price levels. Costs discounted at 3.5%.
a Positive cost difference shows surgery is more costly than angioplasty.

full presentation and discussion of the HRQoL, resource utilisation, and cost-effectiveness studies specified in the protocol.

SLI imposes very serious health and economic burdens in all developed and an increasing number of developing countries. As a result of uncontrolled tobacco consumption and the increasing prevalence of diabetes the global burden of SLI is likely to grow significantly in the future.[2] As with any common and serious condition it is imperative that management decisions are based, wherever possible, on level 1 evidence.

The BASIL trial is the first and only multicentre RCT to compare the clinical effectiveness and cost-effectiveness of surgery and angioplasty in the treatment of this condition and suggests that a bypass-surgery-first strategy should be regarded as the treatment of choice for the 75% of SLI patients who are considered likely to live longer than 2 years. As about three-quarters of the bypasses in the BASIL trial were constructed with autogenous vein, and because it is widely accepted that vein bypasses perform better than those constructed with prosthetic graft material, the strength of this recommendation is greatest in those patients where vein is available as a bypass conduit (see Chapter 5).

Some might argue that the increased survival with bypass surgery observed in the BASIL trial, while reaching statistical significance, is not clinically meaningful. However, this survival advantage for surgery has to be viewed in the context of a condition that has an overall prognosis not dissimilar from many common malignancies.[51] For patients with SLI, many of whom will die of cardiovascular disease, most usually myocardial infarction, within a few years, an additional 6–7

months of life with leg(s) intact seems likely to be viewed as an important benefit worth paying for (see the cost-effectiveness analysis in Chapter 7).

The BASIL trial also suggests that those SLI patients who are unlikely to live for 2 years are probably better served by an angioplasty-first strategy, especially if the alternative is a prosthetic bypass (see Chapter 5). This is because patients with such poor prognosis are unlikely to survive to reap the longer-term benefits of surgery, may be more likely to suffer surgical morbidity and mortality, and because angioplasty is significantly less expensive than surgery in the short term. In Chapter 4 we present a statistical model that can be used to estimate the probability of an individual patient surviving for up to 2 years.

The strengths and weaknesses of the BASIL trial are further discussed in Chapter 10.

Chapter 4

Predicting patient outcomes to assist clinicians deciding on patient-specific treatment strategies

Introduction

An interim intention-to-treat analysis of short-term data from the BASIL trial comparing the survival of patients randomised to bypass surgery or balloon angioplasty showed no significant difference between the two groups out to 2 years from randomisation (see Chapter 2). However, a final intention-to-treat analysis of longer-term follow-up data has shown that those patients who survive 2 years and who were initially randomised to surgery gain a significant c. 7 months of additional life (95% CI 1 month to 13 months) and an additional non-significant c. 6 months of amputation-free life (95% CI 0 months to 12 months) over the subsequent follow-up from 2 years to 7 years 9 months from randomisation (see Chapter 3). This novel level 1 evidence suggests that the clinical decision as to whether surgical or radiological treatment is more appropriate for the treatment of SLI caused by infrainguinal disease should be guided to a significant extent by the chances of the patient surviving for more than 2 years. The aim of the present analysis, therefore, is to examine baseline factors affecting the outcome of the trial cohort as a whole to identify that group of patients unlikely to survive for 2 years and hence to enjoy the longer-term benefit of surgery. In addition, it would be clinically useful to be able to identify those patients whose prognosis is so poor that revascularisation might be considered inappropriate in favour of primary amputation or continuing medical care only.

Methods

Overview

The BASIL trial methods have been described in Chapters 2 and 3 and published elsewhere[50] and the clinical end points were AFS (i.e. patient alive without amputation of trial leg at transtibial level or above) and OS. Detailed clinical data were collected at baseline (see trial forms in Appendix 3) and the preintervention angiograms were scored according to the Bollinger method (infrainguinal segments) and the TASC II criteria (see Chapter 6).[51,52]

Statistical analysis

For the survival analyses patients with no report of death were taken as censored at the end of February 2007 if their death information was from the ISD, at the end of July 2007 if their death information was from the ONS, or at the date of last clinical contact if it was after this date. In addition, four patients who were lost to follow-up and who were thought unlikely to have their deaths recorded in the UK were censored at their last follow-up times; all within 1 year 1 month of randomisation. The potential predictors that were used in the survival analyses were all measured at the time of randomisation, before the patients' assigned treatments were known. The initial set of predictors selected included those that were specified as covariates in the trial protocol. For these predictors we undertook descriptive, univariate and multivariate analyses within a Cox proportional hazards model.

Parametric survival model for up to 2 years from the decision point

To predict how a future patient might behave in terms of OS up to 2 years from randomisation a parametric survival model was developed. Only survival up to 2 years from randomisation was used, with all survivors beyond this time censored at 2 years. This model used the predictors defined in the protocol and a further set of four variables identified in the baseline data that were considered as potential predictors. A simpler model was obtained from these potential predictors by a combination of backward selection and the plausibility of the associations revealed. This approach runs the risk of over-fitting the

model, such that the predictions are more extreme than are justified by the data. To overcome this, the model was developed on a training data set which consisted of a randomly selected 75% of the original data. A shrinkage factor was then calculated that corrects the model for over-fitting, and the predictions were validated on the remaining 25% of the data. A similar approach could have been used for AFS and the results would have been very similar in terms of the ordering of the prognostic factors identified. A Weibull parametric survival model was used because it has a hazard function that can either increase or decrease with time from randomisation (please see below). Specifically, the Weibull model estimates a shape parameter and a linear predictor which together can be used to calculate the predicted survival to a given time for any combination of baseline characteristics. The probability of surviving to time t can be written as $S(T) = \exp\{-[t \exp(-\eta)]^s\}$, where s is the shape parameter and η is a linear predictor calculated from the baseline characteristics. A shape parameter of 1.0 gives a model with constant hazard (exponential distribution of survival times) while a shape parameter below 1.0 indicates a hazard that is decreasing over the follow-up period.

Results

Amputation-free survival and overall survival

The numbers of amputations and deaths before and after 2 years from randomisation are shown in Table 14.

Figure 10(a) shows the survival curves for all patients to amputation or death, or to death. After the first 1–2 years of follow-up the two curves are fairly parallel, indicating that there are few new amputations at this length of time from randomisation.

The smoothed estimates of the hazard functions (Figure 10b) show that the number of amputations in the first year and a half increases the 'amputation or death' hazard compared with that for death only, whereas after that time there are few extra amputations to increase the hazard of 'amputation or death' compared with death. Note also that the initially very high hazards for both end points decline over the first 2 years and appear to become fairly constant after the first 2 years.

This reducing risk is shown by the numbers of amputations during follow-up: 61, 5, 7, 3 and 3 in years 1 to 5, respectively.

Relationship between overall survival and baseline clinical factors

The results of the univariate and multivariate Cox proportional hazard models for AFS and death from any cause over the whole follow-up period are shown in Tables 15 and 16. The baseline factors that remained significant for OS in the multivariate Cox model were in descending order of importance:

- BASIL randomisation stratification group
- below-knee Bollinger scores
- body mass index (BMI)
- age
- diabetes, type I and type II together
- creatinine
- smoking.

The survival curves to death by each of these factors is shown in Figure 11(a to g) and Figure 11(h) shows the survival by randomised treatment on the same scale for comparison. In most cases the association of the factors with survival was in the expected direction and was similar in the univariate and the multivariate analyses. The exceptions were BMI and smoking. A high BMI was associated with better survival in both the univariate and multivariate analyses. In the univariate analysis current smokers had survival similar to never

TABLE 14 *Total events and follow-up time*

Follow-up period	Number of patients undergoing major limb amputation or dying (before major limb amputation)	Total years of follow-up to this end point	Number of deaths	Total years of follow-up to death
Randomisation to 2 years	172	658	131	736
After 2 years from randomisation	108	734	119	863

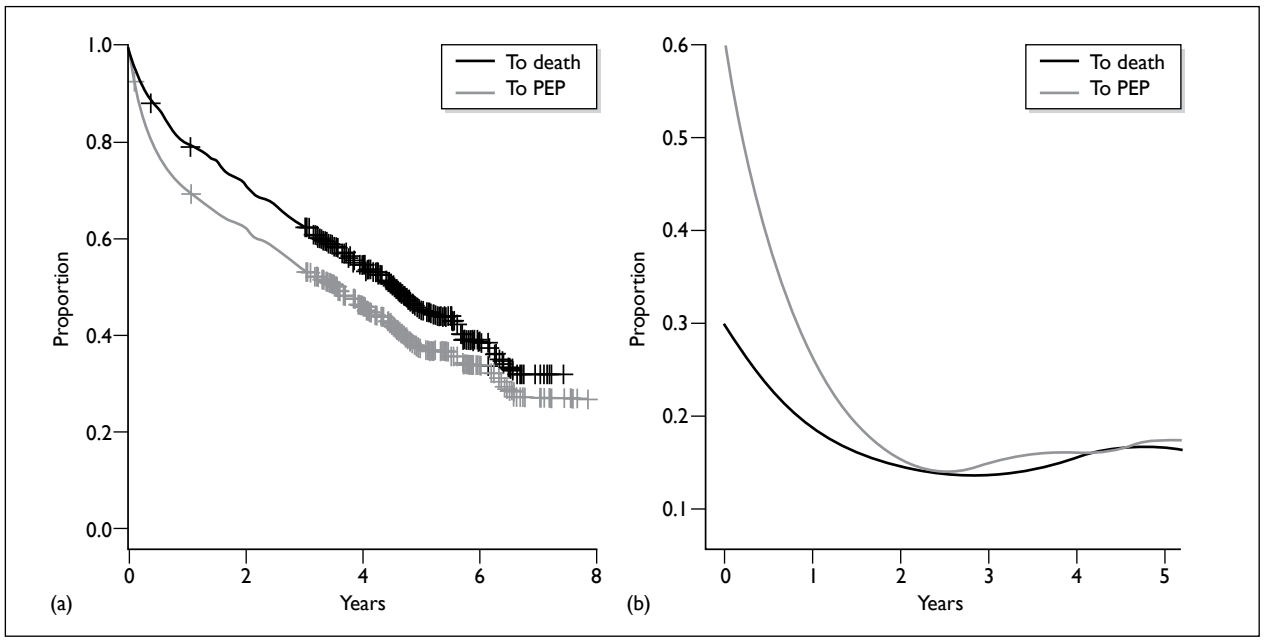


FIGURE 10 *Amputation-free survival (primary end point) and overall survival for whole BASIL trial cohort presented as (a) survival curves and (b) smoothed hazard for each event. The vertical lines on the survival curve (a) indicate that an observation is censored. PEP, primary end point = amputation-free survival (i.e. amputation or death, whichever comes first).*

smokers and ex-smokers had poorer survival but in the multivariate analysis the association was as expected with the current smokers and ex-smokers both having worse survival than non-smokers. This further supports the suggestion that the ex-smoker category has a favourable predicted survival from other factors that improves their survival in the univariate analysis. The time dependence of each of the covariates was checked in the multivariate model using a test for the correlation of the weighted residuals with time.[57] The above-knee Bollinger mean angiogram score was the only factor to show time dependence but the effect was small and probably a false-positive result, given the large number of effects examined.

The effect of randomised treatment

The significant survival advantage, after 2 years, for patients randomised to surgery can be seen in Figure 11(h). The opposite is true in the earlier period, although this was not a significant difference. For the whole time period the test for a time-dependent hazard was significant at $p = 0.028$.[57] This suggests that, given the current evidence, the clinical decision as to whether surgical or radiological treatment is more appropriate should be guided by the chances of the patient's surviving for more than 2 years. We have developed a model that looks at this directly. Compared with the effect of the other covariates the effect of randomised treatment is small and for all practical purposes can be ignored for predicting survival up to 2 years. The randomised treatment was not, therefore, included in the prognostic model.

The reviewers have questioned the decision to omit randomised treatment from the model. They suggest that it is not a question of significance in the data set at hand, it is a structural component in the data, and should really be included. We considered its inclusion when we were planning this analysis but, as described above, because the effect of treatment was so small compared with that of other factors, we decided that it would be simpler to omit it from the model. We did check this assumption post hoc and found that having included treatment made almost no difference to the ranking of cases.

The reviewers have raised some concerns about the amount of missing data. They ask how this arose and what we did analysis-wise; they suggest that if this was a complete case only, then the cumulative missingness across all these variates could have led to a substantial deletion of subjects in the models. We agree that the level of missingness is quite high in certain areas although overall we believe that the completeness of the data compares favourably with other studies in this field. In the analysis a

TABLE 15 *Hazard ratios from Cox proportional hazards model of time to primary end point (amputation-free survival)*

		Univariate analysis			Multivariate analysis		
	No.	**Hazard ratio**	**95% CI**	***p*-value**	**Hazard ratio**	**95% CI**	***p*-value**
Stratification							
Tissue loss and ankle pressure ≥ 50 mmHg (C)	222	2.63	1.77 to 3.89		2.29	1.52 to 3.44	
Ankle pressure < 50 mmHg (B and D)	137	3.70	2.47 to 5.56		2.80	1.81 to 4.34	
No tissue loss and ankle pressure ≥ 50 mmHg (A)	93	Base		< 0.001			< 0.001
Creatinine (log values)							
Low	148	1.21	0.89 to 1.65		1.26	0.91 to 1.73	
High	143	1.95	1.45 to 2.62		1.84	1.36 to 2.51	
Missing	21	1.07	0.57 to 2.03		1.60	0.82 to 3.12	
Medium	140	Base		< 0.001			0.001
Body mass index							
Underweight	51	1.30	0.87 to 1.92		1.38	0.91 to 2.08	
Overweight	115	0.91	0.66 to 1.25		0.96	0.69 to 1.35	
Obese and severely obese	53	0.74	0.48 to 1.16		0.74	0.47 to 1.18	
Missing	85	1.24	0.90 to 1.71		1.18	0.85 to 1.65	
Desirable range	148	Base		0.095			0.191
Diabetes types 1 and 2 together	190	1.50	1.19 1.90	0.001	1.43	1.09 to 1.87	0.009
Age group							
70–79 years	193	1.58	1.19 to 2.11		1.36	0.99 to 1.85	
≥ 80 years	112	1.67	1.21 to 2.30		1.35	0.94 to 1.95	
< 70 years	147	Base		0.002			0.124
Smoking							
Ex-smoker	199	1.27	0.92 to 1.76		0.78		
Current smoker	164	1.10	0.78 to 1.54		1.47	0.59 to 1.03	
Non-smoker	89	Base		0.291		1.05 to 2.07	0.071
Statin (usage vs non-usage)	152	0.77	0.60 to 1.00	0.048	1.66	1.13 to 2.43	0.022
Mean below-knee Bollinger angiography score							
5–8	131	1.37	1.01 to 1.85		1.23	0.90 to 1.69	
> 8	129	1.71	1.28 to 2.30		1.60	1.14 to 2.23	
Missing	34	0.98	0.57 to 1.67		1.59	0.34 to 7.42	
< 5	158	Base		0.002			0.023
Mean above-knee Bollinger angiography score							
5–8	165	1.18	0.88 to 1.59		1.12	0.81 to 1.54	
> 8	119	1.28	0.94 to 1.75		1.14	0.80 to 1.62	
Missing	34	0.86	0.50 to 1.47				
< 5	134	Base		0.269			0.722
TASC II group							
C	186	0.84	0.62 to 1.15		1.01	0.71 to 1.43	
B	122	0.76	0.54 to 1.06		0.93	0.64 to 1.37	
A (best)	12	0.61	0.29 to 1.27		0.58	0.27 to 1.27	
Missing	39	0.63	0.37 to 1.07		0.75	0.17 to 3.24	
D (worst)	93	Base		0.289			0.654

TABLE 16 *Hazard ratios from Cox proportional hazards model of time to death*

		Univariate analysis			Multivariate analysis		
	No.	**Hazard ratio**	**95% CI**	***p*-value**	**Hazard ratio**	**95% CI**	***p*-value**
Stratification							
Tissue loss and ankle pressure ≥ 50 mmHg (C)	222	2.60	1.69 to 3.99		2.13	1.37 to 3.32	
Ankle pressure < 50 mmHg (B and D)	137	3.75	2.41 to 5.82		2.77	1.73 to 4.42	
No tissue loss and ankle pressure ≥ 50 mmHg (A)	93	Base		< 0.001			< 0.001
Creatinine (log values)							
Low	148	1.08	0.77 to 1.49		1.17	0.83 to 1.65	
High	143	1.78	1.30 to 2.43		1.64	1.19 to 2.26	
Missing	21	1.04	0.53 to 2.02		1.46	0.73 to 2.91	
Medium	140	Base		0.001			0.021
Body mass index							
Underweight	51	1.29	0.86 to 1.96		1.43	0.93 to 2.20	
Overweight	115	0.82	0.59 to 1.15		0.91	0.64 to 1.30	
Obese and severely obese	53	0.52	0.31 to 0.86		0.54	0.32 to 0.91	
Missing	85	1.21	0.87 to 1.69		1.11	0.79 to 1.57	
Desirable range	148	Base		0.005			0.023
Diabetes types 1 and 2 together	190	1.32	1.03 1.70	0.027	1.37	1.03	0.032
Age group		0.00					
70–79 years	193	1.84	1.34 to 2.51		1.47	1.05 to 2.05	
≥ 80 years	112	2.20	1.56 to 3.11		1.68	1.14 to 2.49	
< 70 years	147	Base		< 0.001			0.021
Smoking							
Ex-smoker	199	1.37	0.97 to 1.93		1.61	1.12 to 2.30	
Current smoker	164	1.02	0.71 to 1.47		1.53	1.02 to 2.28	
Non-smoker	89	Base		0.063			0.025
Statin (usage vs non-usage)	152	0.75	0.57 0.98	0.036	0.79	0.59	0.109
Mean below-knee Bollinger angiography score							
5–8	131	1.63	1.19 to 2.25		1.43	1.02 to 2.00	
> 8	129	1.87	1.37 to 2.55		1.62	1.14 to 2.30	
Missing	34	0.90	0.49 to 1.66		1.81	0.37 to 2.28	
< 5	158	Base		< 0.001			0.018
Mean above-knee Bollinger angiography score							
5–8	165	1.30	0.95 to 1.77		1.31	0.93 to 1.83	
> 8	119	1.30	0.93 to 1.81		1.34	0.92 to 1.94	
Missing	34	0.75	0.41 to 1.39				
< 5	134	Base		0.118			0.206
TASC II group							
C	186	0.73	0.53 to 1.01		0.79	0.54 to 1.14	
B	122	0.81	0.57 to 1.15		0.98	0.66 to 1.46	
A best	12	0.62	0.29 to 1.30		0.63	0.29 to 1.39	
Missing	39	0.53	0.29 to 0.95		0.60	0.14 to 2.58	
D (worst)	93	Base		0.157			0.456

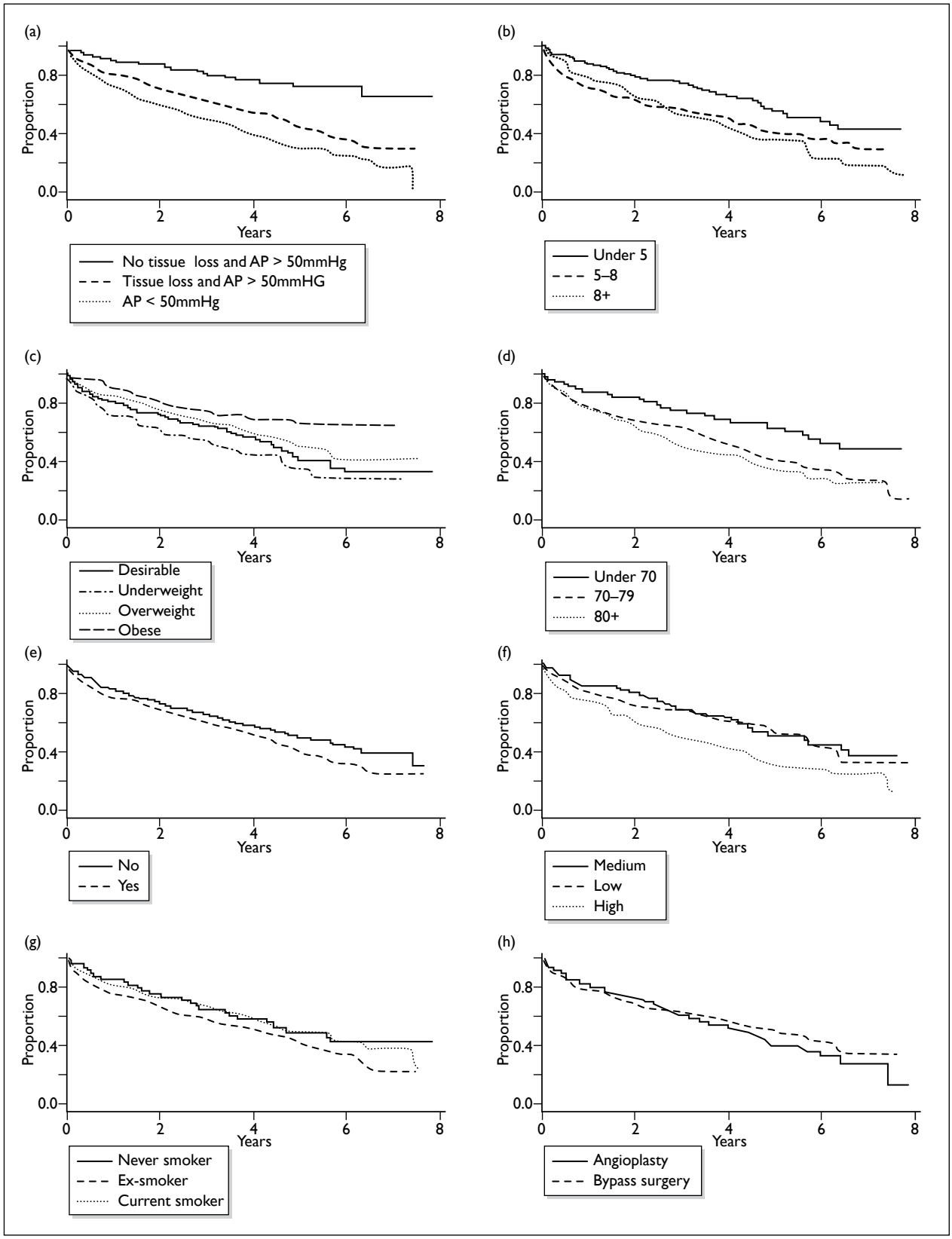


FIGURE 11 *Survival to death by baseline covariates. (a) BASIL randomisation stratification group; (b) mean below-knee Bollinger angiography score; (c) body mass index; (d) age; (e) diabetes types 1 and 2 together; (f) log serum creatinine; (g) smoking status; (h) treatment allocation at randomisation. AP, ankle pressure.*

TABLE 17 *Relationship between number of ankle pressures measurable and highest ankle pressure in the trial leg*

No. of ankle pressures measurable using hand-held Doppler ultrasound	Highest ankle pressure (mmHg)					
	≥ 100	75–100	51–74	0–50	Not measurable	All
None	0	0	0	0	75	75
One	12	33	56	52	0	153
Two	31	71	57	24	0	183
Three	16	17	7	1	0	41
All	59	121	120	77	75	452

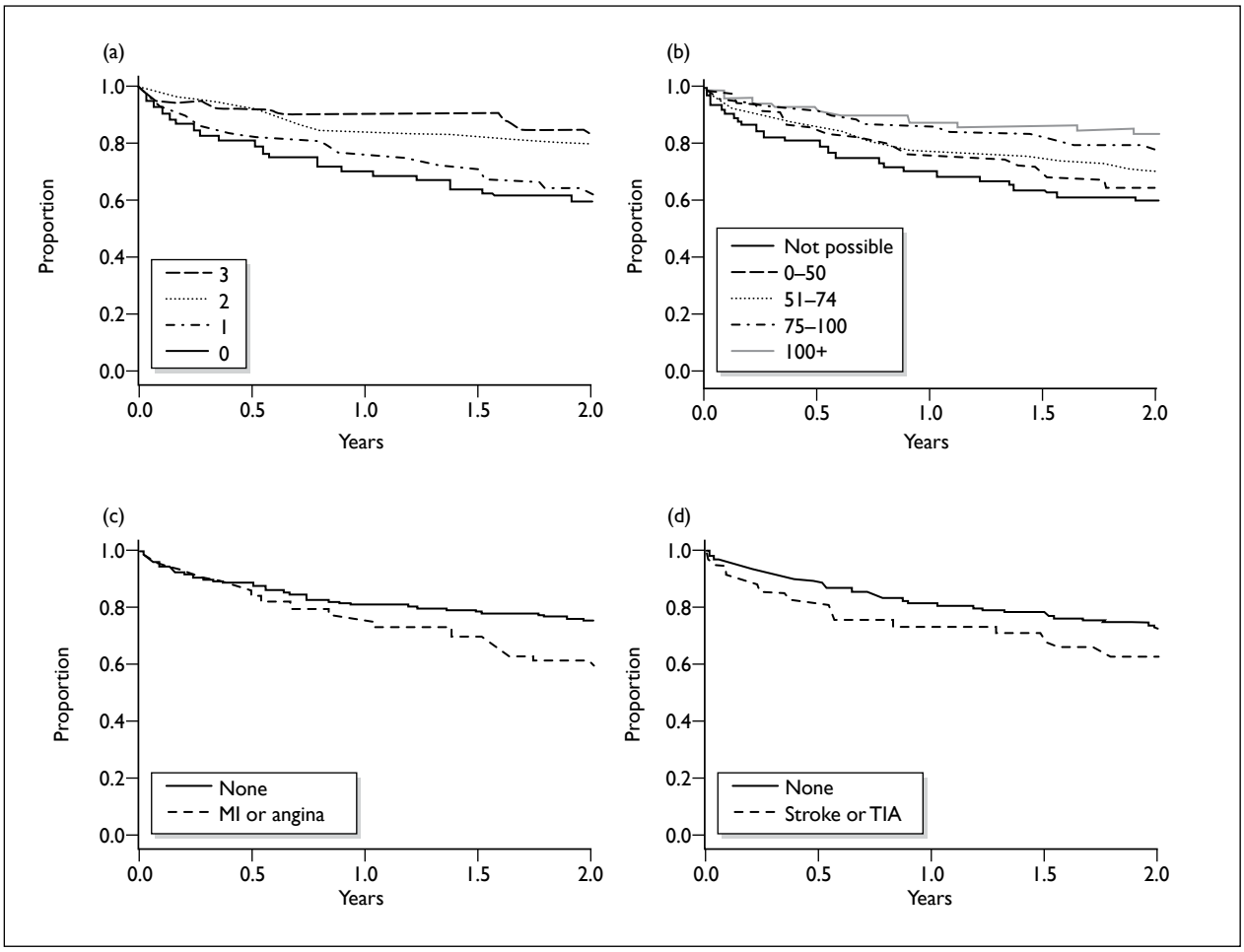


FIGURE 12 *Overall survival to 2 years by (a) number of ankle pressures measurable using hand-held Doppler ultrasound, (b) highest ankle pressure measurable (mmHg), (c) history of myocardial infarction (MI) or angina, and (d) history of stroke or transient ischaemic attack (TIA).*

missing data category was used for variables with a substantial amount of missing data. This approach has been criticised when the focus of interest is the covariate, but where it is being used as an adjustment it is, we respectfully suggest, considered an acceptable approach.

Modelling overall survival to 2 years from randomisation

The baseline data described above that were used to adjust for the effect of treatment in the main end point analysis (see Chapters 2 and 3) were further examined to determine if there were any other factors that could improve the predictive model. Three further factors were selected:

- number of ankle pressures measurable using hand-held Doppler ultrasound
- a history of myocardial infarction or angina
- a history of stroke or transient ischaemic attack.

With regard to the first of these, examination of the ankle pressure data showed that there were many cases where one or more of the three possible ankle pressures (dorsal pedis, posterior tibial and peroneal) were classed as 'not recordable'. In general, as might be expected, there was a positive relationship between a low ankle pressure and 'missing' ankle pressures (Table 17).

Figure 12(a) illustrates the survival to death curves up to 2 years by the number of ankle measurements obtained. The final ankle pressure was defined in the protocol as the maximum of the values obtained. Figure 12(b) shows the survival to death by a finer grouping of the pressure values for those where a measurement was possible.

The stratification indicator at randomisation was replaced by these two ankle pressure measures (the highest ankle pressure obtained and the number of measurements obtained) and whether tissue loss was present (considered separately). The number of ankle pressure measures was considered as an unordered category. The two clinical histories (myocardial infarction or angina, stroke or transient ischaemic attack) were added as possible contributors to the prognostic model. Statin use was excluded because although in the BASIL trial only approximately one-third of patients were on cholesterol-lowering therapy, in 2009 almost all patients with SLI would be prescribed a statin as part of 'best medical therapy'.[3] TASC II and the Bollinger above-knee angiography score were excluded as the below-knee Bollinger score was the stronger independent predictor.

Figure 12(c,d) illustrates the OS to 2 years by a history of myocardial infarction/angina or stroke/transient ischaemic attack.

A parametric overall survival model for up to 2 years from the decision point

A training data set was selected that consisted of a random selection of 75% of the original data (339 cases, 98 deaths) leaving the other 113 cases (33 deaths) to form a validation data set. When the data set is of limited size, the choice of which proportions to use in the training and validation data sets is difficult. A training set with too few cases may yield a poor prediction and a validation data set with too few may make the interpretation of the validation results difficult. We decided that the former was more important and so selected a larger training data set.

Starting with all the variables mentioned above, we attempted to find a simpler model that might fit the data better.

The procedure was to use backward elimination with the option to remove any variables for which the grouped p-value (for categories) was greater than 0.1. However, each case was considered in terms of the plausibility of the coefficients for the individual groups and retained if these seemed clinically reasonable and important. Continuous variables replaced groupings where effects appeared linear.

One particular decision is worth highlighting. The ankle pressure data were initially fitted as two categorical variables as illustrated in Figure 12. With all the other variables in the model the groups for ankle pressure did not approach statistical significance. However, the coefficients for the groups showed a clear dose–response relationship, with the lowest group having the worst survival. It was therefore decided to include the ankle pressure in the model as a continuous variable, because of its clinical plausibility, even though its p-value (two-sided) for including in the final model was only 0.25. Formally the ankle pressure value was replaced with zero when no measurements were taken, but the choice of value for those not measured does not affect the prediction when the

number of ankle pressure measures is included in the prediction model.

The final model differed from the full model in that:

- Age was fitted as a continuous variable (range 39 to 99 years in the BASIL cohort).
- The number of ankle pressure measurements obtainable (range 0–3) was fitted as a categorical variable.
- The ankle pressure was taken as a continuous variable, set to zero if no pressure available.
- Below-knee Bollinger angiography scores were simplified to an average value < 5 or ≥ 5.
- Diabetes was excluded since it was no longer predictive once all the other variables were included.

The coefficients in the linear predictor for the training data set and the full data set are given in Table 18.

Model validation

When data are used to select a model the predictions will tend to be too extreme. We can correct for this by shrinking the individual predictions towards the mean. A very reasonable approximation to an appropriate shrinkage can be obtained by calculating a shrinkage factor as discussed by Copas.[58] This is calculated as $[1-(df-2)/k]$, where 'df' is the residual degrees of freedom used in fitting the model and k is the overall value of the chi-squared statistic for the final model. The linear predictors are then shrunk towards the mean value for the linear predictor by this factor. For this example a shrinkage factor of around 0.75 is obtained. We can check how well this shrinkage factor will correct any over-fitting by examining the fit obtained for the validation set. Linear predictors for the fitted model were obtained for the training and validation data sets and in each case three equal-sized groups were formed to make high, medium and low groups.

Figure 13(a) compares the modelled survival for the three groups based on the training data with the empirical survival curves. The fit is excellent. For the smaller validation data set the fit is poorer, as we would expect, and in particular it is too optimistic for the groups with good survival (Figure 13b). The shrunken estimates (Figure 13c) correct this. Although they appear to under-fit the poor prediction group, this could just be a chance effect because of the small size of the prediction data set. We recommend the shrunken predictor, with a shrinkage factor of 0.75 be used for individual predictions.

Predicting overall survival for future individual patients: a parametric overall survival model for up to 2 years from the decision point

Figure 14 shows a histogram of the probability of surviving to 2 years for the 452 patients randomised. We can see that, although there is a wide spread of probabilities of surviving to 2 years there are substantial numbers with a good prognosis. In particular, 52% of patients have a probability of survival to 2 years of 0.75 or more and 21% above 0.85. At the other extreme 19% of patients have a probability of less than 0.6 of surviving to 2 years based on their baseline characteristics.

The information in Table 18 and the shrinkage factor can be used to calculate an individual linear predictor for any combination of covariates. Although the model was developed and validated from the training data set, it would seem sensible to make predictions for future patients from all the data available. This linear predictor can then be shrunk towards the mean of the all the predictors which has a value of 2.52 for prediction from the full data. The formula for the shrunken predictor then becomes $2.52 + 0.75 \times$ (linear predictor – 2.52). The probability of surviving to any time up to 2 years, from the decision point, can then be readily calculated from the Weibull survival function with a shape parameter of 0.637.

Table 19 illustrates the predicted outcomes for several BASIL trial patients from across the range of prognostic scores.

Discussion and conclusions

The BASIL trial has shown that those patients who survive 2 years and who were initially randomised to bypass surgery gain a significant c. 7 months of additional life (95% CI 1 month to 13 months) and an additional non-significant c. 6 months of amputation-free life (95% CI 0 months to 12 months) over the subsequent follow-up from 2 years to 7 years 9 months from randomisation when compared with those initially randomised to angioplasty (see Chapters 2 and 3). A fundamental question, therefore, that clinicians may wish to

TABLE 18 *Fitted linear predictor for the Weibull model (positive coefficients indicate better overall survival)*

	From training data ($n = 339$)			From full data ($n = 452$)		
	Coefficient	**Standard error**	***p*-value**	**Coefficient**	**Standard error**	***p*-value**
Intercept	7.5173	1.9591	0.000	8.0978	1.6526	0.000
Tissue loss	–1.0076	0.4965	0.042	–0.8022	0.3765	0.033
Creatinine						
Low (< 88)	–0.7211	0.4442	0.105	–0.8176	0.3672	0.026
High (>115)	–0.5540	0.4448	0.213	–0.7579	0.3582	0.034
Missing	–0.9508	0.8279	0.251	–0.9773	0.7357	0.184
Medium (88–115)	Reference category					
Age(per year)	–0.0402	0.0223	0.071	–0.0493	0.0184	0.007
Mean below-knee Bollinger angiography score						
< 5	–0.5761	0.4173	0.167	–0.4798	0.3231	0.138
Missing	–0.3269	0.7343	0.656	–0.0529	0.6113	0.931
≥ 5	Reference category					
Smoking						
Ex-smoker	–0.9940	0.4623	0.032	–1.0895	0.3766	0.004
Smoker	–0.7838	0.5259	0.136	–0.8427	0.4220	0.046
Non-smoker	Reference category					
BMI						
Underweight	–0.7086	0.5109	0.165	–0.5839	0.3997	0.144
Overweight	0.0063	0.4431	0.989	0.0247	0.3644	0.946
Obese	1.4336	0.7347	0.051	0.7739	0.5280	0.143
Missing	–0.1274	0.4611	0.782	–0.2181	0.3479	0.531
Desirable	Reference category					
Number of ankle pressures measurable using hand-held Doppler ultrasound						
Three	–0.3731	0.6237	0.550	–0.2598	0.4829	0.591
Two	0.5030	0.6987	0.472	0.4233	0.5634	0.452
One	0.6558	1.0380	0.528	0.7943	0.8245	0.335
None	Reference category					
History of MI or angina	–0.8781	0.3706	0.018	–0.7451	0.2814	0.008
History of stroke or TIA	–0.5810	0.3755	0.122	–0.5666	0.2996	0.059
Highest ankle pressure (mmHg)	0.0086	0.0075	0.247	0.0066	0.0060	0.269
Log(1/Shape factor)	0.450	0.095	< 0.001	0.364	0.082	< 0.001
Shape factor	0.6376			0.6949		

BMI, body mass index; MI, myocardial infarction; TIA, transient ischaemic attack.

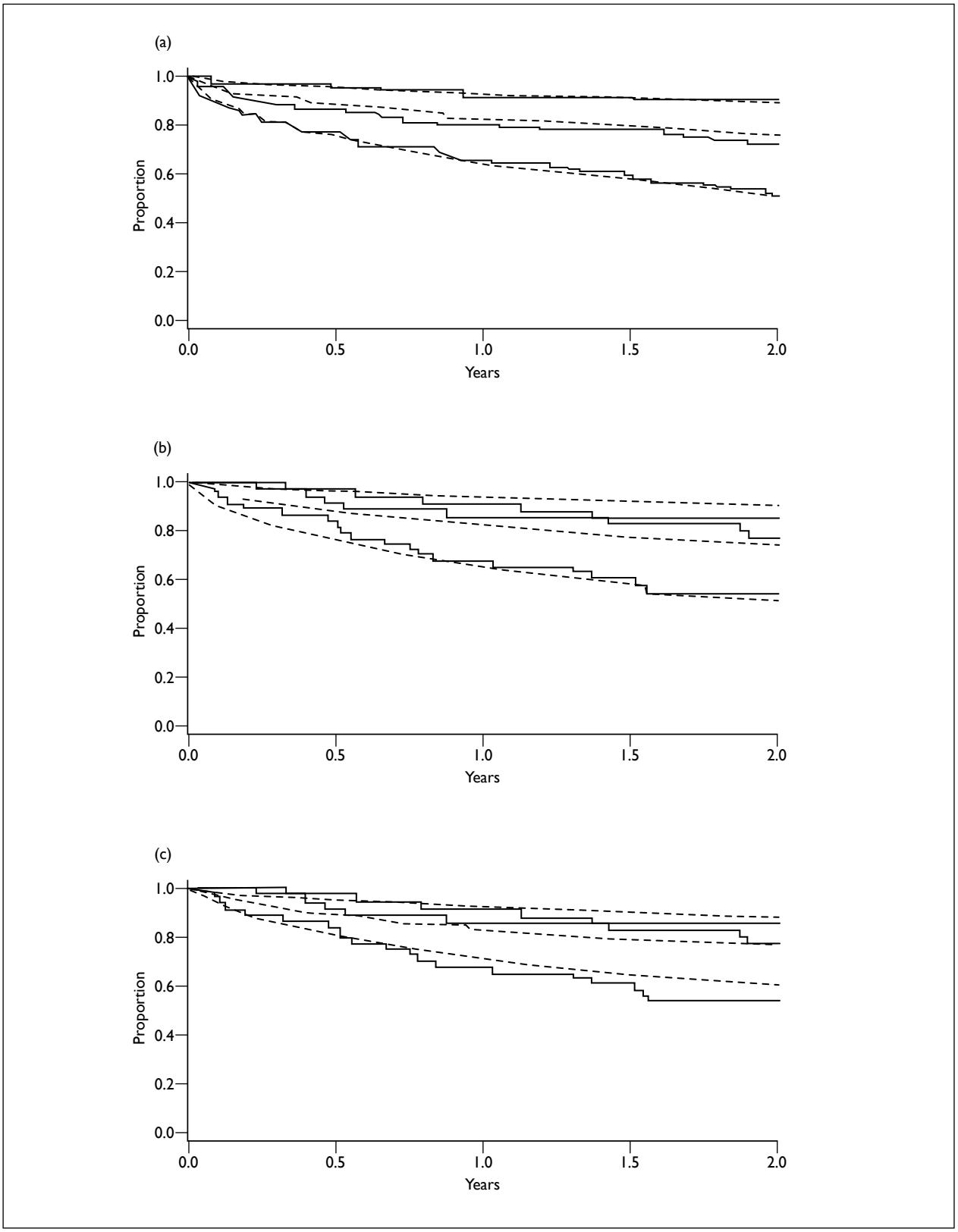


FIGURE 13 *Fits (a) training data, (b) validation data and (c) validation data with shrinkage. In each case the data were grouped into three equal-sized groups according to the value of the linear predictor. The dotted lines show the fitted Weibull survival for the average linear predictor in each group. The solid lines are the Kaplan–Meier survival curves for each group.*

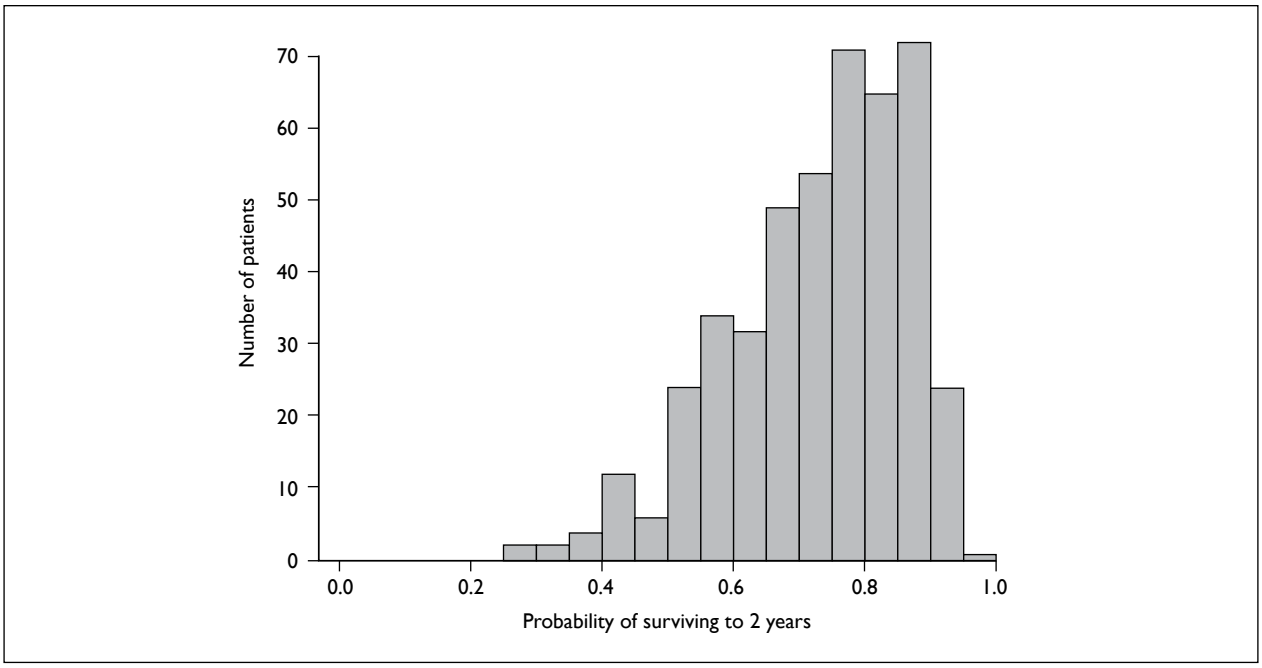


FIGURE 14 *Histogram of the probability of surviving to 2 years (shrunken estimate), 452 randomised patients.*

TABLE 19 *Predicted 6-month, 1-year and 2-year overall survival for five patients based on baseline data entered into the Weibull parametric survival model*

	Five BASIL patients with a range of predicted survivals				
Characteristics	**A**	**B**	**C**	**D**	**E**
Smoker	Ex-smoker	Ex-smoker	Current smoker	Current smoker	Current smoker
Body mass index	Desirable range	Overweight	Desirable range	Underweight	Overweight
Creatinine level	Low	Low	Low	Low	Low
Tissue loss	Yes	Yes	Yes	Yes	No
Number of ankle pressures recorded	None	One	One	Two	All 3
Ankle pressure	0	60	30	56	136
Below-knee Bollinger score	≥ 5	Missing	< 5	< 5	< 5
History of MI/angina	Yes	No	Yes	No	No
History of stroke/TIA	No	No	No	No	No
Age	79	80	63	56	59
Predicted % surviving to					
6 months	71	84	90	97	97
1 year	57	75	84	96	95
2 years	40	63	76	93	92

MI, myocardial infarction; TIA, transient ischaemic attack.

TABLE 20 *A representation of a 'screen-shot' from an Excel spreadsheet containing the modelling equations; this can be used by clinicians to determine predicted survival for individual patients (to be made available at www.basiltrial.com)*

Use menus or enter values in grey cells to describe the case of interest			
Patient characteristics		**Results**	
Tissue loss	Yes	Time from decision	Proportion surviving
BMI	20–25	6 months	71%
Creatinine	Low	1 year	57%
Bollinger below-knee angiogram score	≥ 5	2 years	40%
Age	79		
Smoking	Ex-smoker		
Any history of MI/angina	History of MI		
Any history of stroke/TIA	No history of stroke/ TIA		
Number of ankle pressures measurable with hand-held Doppler ultrasound	0		
Highest measurable ankle pressure (mmHg)	0		

BMI, body mass index; MI, myocardial infarction; TIA, transient ischaemic attack.

address when deciding how to treat those of their SLI patients who are potentially suitable for both surgery and angioplasty, is: will this patient live long enough (it is suggested more than 2 years) to enjoy the benefits of bypass surgery? The present study shows that, almost regardless of what treatment is offered, patients with SLI demonstrate poor outcome in terms of AFS and OS. At the end of follow-up, just over a third of patients were alive without major limb amputation of the trial leg and fewer than half were alive. Although the majority of amputations and deaths occurred in the first year after randomisation, the high event rate continued at between 10% and 20% per survivor-year thereafter.

However, by exploring a wide range of baseline clinical and angiographic (see Chapter 6) factors, all easily obtainable in routine clinical practice, it has proved possible to develop a prognostic model for survival of BASIL and 'BASIL-like' patients up to 2 years from randomisation.

Prediction models can be affected by over-fitting that makes their predictions appear too extreme when they are evaluated on the same data that were used to develop the model. To correct for this, a shrunken model was developed that describes how the model will perform on new data. The most important predictors were age, presence of tissue loss, smoking and a history of angina or myocardial infarction. Other factors include serum creatinine, history of stroke or transient ischaemic attack, below-knee Bollinger score (see Chapter 6), body mass index, number of recordable ankle pressure measurements and the highest ankle pressure.

Together, these factors can be used to try to identify patients who are unlikely to live for more than 2 years after intervention and who, therefore, may be unlikely to enjoy longer-term benefits of surgery. The model has been incorporated into an Excel spreadsheet that can be used to predict survival to 6 months, 1 year and 2 years for future patients (to be made available at www.basiltrial.com) (Table 20).

The reviewers have suggested that the current analysis does not inform as to whether the model is useful in terms of predicting who should be treated with surgery. They suggest that 'the current analysis should have been extended to create a decision rule, e.g. treat if risk probability > x, and that we then need to see the "diagnostic properties" – the sensitivity, specificity, false positive, false negative, area under the ROC curve metrics – to get a feel for how useful the model is.' We respectfully suggest that taking this analysis forward as suggested might risk us being criticised for trying to overanalyse and overinterpret the data.

The strengths and weaknesses of the prediction model as we view them ivn the context of the overall BASIL trial results are further discussed in Chapter 10.

Chapter 5
On-treatment analyses

Introduction

Severe leg ischaemia, characterised by rest/night pain and tissue loss (ulceration, gangrene), leads to significant morbidity and mortality as well as to the consumption of considerable health and social care resources, in developed and developing countries. The BASIL trial remains the only multicentre RCT to have compared bypass-surgery-first and balloon-angioplasty-first revascularisation strategies for the treatment of SLI due to infrainguinal disease.

Interim (see Chapter 2) and final (see Chapter 3) intention-to-treat analyses of the BASIL trial performed in 2005 and 2008 respectively have shown that bypass surgery and balloon angioplasty lead to similar AFS and OS (or ACM) up to 2 years from randomisation. However, for those patients who survived for more than 2 years after intervention, initial randomisation to surgery was associated with a significant increase of c. 7 months in restricted mean OS, and a non-significant increase of c. 6 months in restricted mean AFS, during the subsequent mean follow-up of 3.1 years (range 1 to 5.7 years). Hospital costs and HRQoL were not significantly different between the two groups over the first 3 years.

These findings, based on an intention-to-treat analysis of randomised data, suggest that patients who could be treated by either balloon angioplasty or surgery and who are expected to live more than 2 years should usually be considered for bypass surgery first while those not expected to survive beyond 2 years should normally be considered for balloon angioplasty in the first instance.

Although the majority of the BASIL trial patients received their assigned treatment in a timely fashion, as was to be expected, interventions were sometimes delayed, sometimes the opposite treatment was undertaken, and a small number of patients received no revascularisation for a variety of different reasons. The rate of subsequent secondary and crossover interventions was also high, reflecting the complex patient journeys often observed in the management of this condition.

By-treatment-received analyses of RCTs have to be undertaken with great care because the rigour of randomisation has been lost and a degree of bias is therefore inevitable (see Chapter 10). However, surgical and interventional colleagues have urged us strongly to undertake a by-treatment-received analysis of the BASIL data. We recognise that, provided the results are interpreted with caution, such an approach is appropriate and may increase the value of the trial to clinicians managing these challenging patients.

In this chapter, therefore, we present an analysis of the main clinical outcomes (AFS, OS) by first intervention received, and describe the nature and timing of first interventions and reinterventions. We also compare vein with prosthetic bypass and transluminal with subintimal angioplasty; and examine outcomes from bypass surgery after failed angioplasty.

Methods

The trial methods have already been described in detail in Chapters 2 and 3.

Briefly, between August 1999 and June 2004 consultant vascular surgeons and interventional radiologists in 27 UK hospitals randomised 452 patients with SLI, defined as rest pain and/or tissue loss (ulcer and/or gangrene) of (infrainguinal) arterial aetiology present for more than 2 weeks, who on diagnostic imaging had a pattern of disease which, in their joint opinion, could equally well be treated by either infrainguinal bypass surgery or balloon angioplasty, to either a 'bypass-surgery-first' or a 'balloon-angioplasty-first' revascularisation strategy.

Responsible consultant vascular surgeons and interventionalists were encouraged to undertake the assigned procedure as soon as possible after patient randomisation; permitted to use their normal custom and practice with regard to preintervention assessment, the intervention itself and postintervention follow-up; and asked to record at the end of the procedure whether in their view it had been an immediate technical success.

All patients provided written informed consent and the study was approved by the Multicentre Research Ethics Committee for Scotland. The BASIL trial was registered with the National Research Register and the International Standard Randomised Controlled Trials Number Scheme (ISCRTN45398889).

Data on all first interventions and reinterventions were prospectively collected as were those on amputation of the trial limb at transtibial level or above and death from any cause. For the first year of follow-up, six dedicated research nurses travelled regularly to trial centres to collect data on randomised patients. Thereafter, the data were collected locally by the vascular teams. The trial co-ordinator liaised continually with these teams and travelled at least annually to trial centres to collect data from paper-based and electronic hospital information systems regarding further procedures and primary outcomes. Where necessary we also contacted primary-care doctors and nurses. In addition, end point data (deaths, amputations, further procedures) were collected through national audit mechanisms.

Details of patients recruited in Scottish centres were also logged with the ISD of the NHS in Scotland. All patients alive at the end of follow-up had their status confirmed by linkage to the GRO(S) (Scotland) or the ONS (England) death records. Hospital admissions for Scottish patients were obtained by record linkage to Scottish Morbidity Records (SMR1). All patients have been followed for 3 years and over half for 5 years. Preintervention angiograms were scored using the Bollinger system by a panel of surgeons and radiologists blind to the treatment received and the patients' outcome.

For the survival analyses patients with no report of death were taken as censored at the end of February 2007 if their death information was from ISD; or at the end of July 2007 if their death information was from ONS; or at the date of last clinical contact if it was after this date. In addition, four patients who were lost to follow-up and who were thought unlikely to have their deaths recorded in the UK were censored at their last follow-up times; all within 1 year 1 month of randomisation. Comparison of AFS and OS was by log-rank tests. Other associations were assessed by chi-squared tests with tests for trend where appropriate.

Data were collected for every major or minor procedure carried out during follow-up. These were classified as major surgery, major intervention, minor surgery or minor intervention.

For all major interventions information was recorded as to whether the surgeon or radiologist considered that the procedure had been an immediate technical success. For major surgical or radiological procedures the intervention was considered an early clinical success if it was immediately technically successful and it was not followed within 30 days by a further major intervention (surgical or endovascular), major amputation or death.

Exploratory analyses of the timing of interventions lead to the grouping of the major surgical and radiological interventions to form the different groups as described below. The subsequent survival of these groups to the main end points (major amputation of trial leg, death from any cause) was compared graphically by examination of the Kaplan–Meier survival curves. These were interpreted with reference to the prognosis for the patients in each of these groups, using the model developed in Chapter 4.

Results

Nature and timing of interventions after randomisation

A total of 228 patients were randomised to bypass surgery and 224 to balloon angioplasty. The assigned intervention was attempted during the first year after randomisation in 85% and 96% of those allocated to bypass surgery and balloon angioplasty respectively (CONSORT diagrams showing patient flows into and through the trial are presented in Chapters 2 and 3).

However, some of those interventions were delayed, and the rate of early secondary procedures was also quite high. All interventions undertaken at any time during follow-up (range 3–7 years), including repeat procedures and those carried out as secondary procedures at the same time as the primary procedure, are shown in Table 21.

The cumulative number of treatments received by patients over the first 12 weeks from randomisation is shown in Table 22.

TABLE 21 *All surgical and interventional procedures carried out on trial leg at any time during follow-up (range 3–7 years)*

	All (*n* = 452)	Randomised to balloon angioplasty (BAP) (*n* = 224)	Randomised to bypass surgery (BSX) (*n* = 228)
Revascularisation (interventional)			
BAP[a]	299	243	56
BAP of graft stenosis	31	8	23
Stent	9	7	2
Revascularisation (surgical)			
BSX	266[b]	55	211
BSX and endarterectomy	6	4	2
Endarterectomy and vein patch	7	2	5
Thromboembolectomy	31	17	14
Other	5	4	1
Amputations (major)			
Above knee	40	19	21
Below knee	46	24	22
Minor procedures			
Sympathectomy	6	2	4
Debridement	31	10	21
Other surgery	43	7	28
Skin graft	8	2	1
Amputations (minor)			
Digital amputation	112	42	70
Forefoot amputation	14	5	9

a Excludes two cases where patient taken to angio suite but procedure not attempted.
b Excludes four cases where patient taken to theatre but procedure not attempted.

TABLE 22 *Cumulative treatments received over the first 12 weeks after randomisation*

	Randomised to BAP (*n* = 224)						Randomised to BSX (*n* = 228)					
By end of week from randomisation	1	2	4	6	8	12	1	2	4	6	8	12
No treatment	94	72	42	23	13	9	105	66	38	33	31	23
Randomised treatment only, immediate technical success[a]	104	116	135	148	152	153	111	147	168	170	171	174
Randomised treatment attempted and either not done or immediate technical failure[a]	19	15	18	19	18	17	2	1	2	2	2	2
Only opposite treatment, including immediate technical failures	0	1	1	1	3	3	9	10	12	11	12	13
Randomised then opposite treatment, including immediate technical failures	7	19	24	28	31	35	1	1	2	2	2	2
More than two revascularisation attempts	0	1	4	5	6	7	0	3	6	10	11	14
All	224	224	224	224	224	224	228	228	228	228	228	228

BAP, balloon angioplasty; BSX, bypass surgery.
a Immediate technical success as judged by the responsible consultant surgeon or interventional radiologist.

By 12 weeks after randomisation nine (4%) balloon angioplasty patients versus 23 (10%) bypass surgery patients had not undergone revascularisation; three (1.3%) balloon angioplasty versus 13 (5.8%) bypass surgery patients had undergone the opposite treatment first; and 35 (15.6%) balloon angioplasty and two (0.9%) bypass surgery patients had received the assigned treatment and then undergone the opposite treatment for immediate technical or early clinical failure. Overall, 21 patients underwent more than two attempts at revascularisation during the first 12 weeks after randomisation. However, the rate of new interventions levels off by week 8 after randomisation. We have, therefore, chosen to analyse outcomes according to the interventions received during the first 8 weeks following randomisation. The reasons for no intervention being carried out during the first 8 weeks after randomisation in patients assigned to angioplasty or surgery are shown in Table 23. Table 24 provides further details of all first and subsequent attempts at revascularisation during the first 8 weeks after randomisation by randomised group; the short-term outcome of those attempted revascularisations and the patients' status (amputation, death) at 8 weeks.

Surgery was attempted as a first revascularisation procedure within 8 weeks of randomisation in 185 patients. In 171 patients bypass surgery was immediately technically successful and no further attempt at revascularisation was undertaken during the 8 weeks after randomisation or within 30 days (whichever was the longest). However, by 8 weeks, 12 of these 171 patients were dead and four had undergone major amputation of the trial (operated) leg. In three patients, bypass surgery was judged an immediate technical failure; one patient went on to have no further revascularisation during the 8 weeks after randomisation or within 30 days and two patients went on to have further surgery during this time period; one of these went on to amputation within the 8-week/30-day period. Eight patients had bypass surgery as a first revascularisation that was judged to be an immediate technical success but went on to have balloon angioplasty (seven patients) or further surgery (one patient) during the 8 weeks after randomisation or within 30 days. Two patients had bypass surgery combined with balloon angioplasty as a technically successful first and only revascularisation during the first 8 weeks.

Procedures and outcomes in the 224 patients who underwent balloon angioplasty as the first attempted revascularisation during the first 8 weeks can be found in Table 24 in the same way. Overall, in the first 8 weeks after randomisation, patients randomised to balloon angioplasty were more likely to have their assigned treatment first (208/224, 93% versus 182/228, 80%, p = 0.01, chi-squared test) while those randomised to bypass surgery were more likely to have the opposite treatment first (16/228, 7.0% versus 3/224, 1.3%, p = 0.04, Fisher's test) or no revascularisation (30/228, 13.1% versus 13/224, 5.8%, p = 0.01, Fisher's test).

The number of patients assigned to balloon angioplasty who did not receive their randomised allocation as the first treatment was too small to make comparisons with those that did. However, those that were assigned to bypass surgery and who did and did not receive surgery as their first treatment were not different in terms of five baseline characteristics (age, below-knee Bollinger angiogram score, presence of tissue loss, serum creatinine, numbers of ankle pressures obtainable) that best predict the subsequent OS of the BASIL trial cohort as a whole (see Chapter 4).

TABLE 23 *Reasons for no intervention being carried out during the first 8 weeks after randomisation in patients assigned to angioplasty or surgery*

	Randomised treatment		
Reason	**Angioplasty**	**Surgery**	**Total**
Died/myocardial infarction/deteriorating gangrene	2	5	7
Deemed unsuitable for and/or unable to tolerate the procedure	5	6	11
Refused intervention	1	7	8
Not known	7	13	20
Total	15	31	46

TABLE 24 *Revascularisations undertaken in the first 8 weeks after randomisation by first intervention attempted and randomised group*

First attempted revascularisation	All attempted revascularisations and outcomes[a] in first 8 weeks following randomisation	Patient randomised to: Balloon angioplasty (BAP) (*n* = 224)	Patient randomised to: Bypass surgery (BSX) (*n* = 228)	Total
None	None	13 (A1, D1)	30 (D5)	43
BSX	Taken to theatre but BSX not done		1 (D1)	1
	BSX, nil else	3 (D1)	168 (A4, D11)	171
	BSX combined with BAP, nil else	0	2	2
	BSX, BAP	0	4	4
	BSX, failed BAP	0	2	2
	BSX, failed BAP, BAP	0	1	1
	BSX, BSX	0	1 (D1)	1
	Failed BSX, nil else	0	1	1
	Failed BSX, BSX	0	2 (A1)	2
	All BSX attempted first	3(D1)	182 (A5, D13)	185
BAP	Taken to suite but BAP not done	2 (A1)		2
	BAP, nil else	153 (A4, D7)	11 (D1)	164
	BAP, BSX	7 (A1)		7
	BAP, BSX, BSX	1 (A1)		1
	BAP, BAP		1	1
	BAP, failed BAP	1		1
	Failed BAP, nil else	16 (A3, D2)	2 (A1)	18
	Failed BAP, failed BSX, BSX	1		1
	Failed BAP, BSX	24 (A1, D2)	2	26
	Failed BAP, failed BSX, failed BAP, BSX	1 (A1)		1
	Failed BAP, BAP	2	1	3
	All BAP attempted first	208 (A12, D11)	16 (A1, D1)	224
All	Totals	224 (A13, D13)	228 (A6, D19)	452

BAP, balloon angioplasty; BSX, bypass surgery.

a Outcomes: 'failed' denotes immediate technical failure; 'nil else' denotes immediate technical success and no further revascularisation procedure within the 8 weeks after randomisation or within 30 days of the first revascularisation. Where other revascularisations are listed, these followed the first revascularisation within the 8-week period after randomisation or within 30 days. Numbers in brackets give the status at 8 weeks from randomisation (A, alive with trial leg amputated at transtibial level or above; D, dead).

Patients who had balloon angioplasty as their first attempted revascularisation within the first 8 weeks were more likely to suffer an immediate technical failure (as judged by the responsible interventionalist at the time) or early clinical failure (requirement for further revascularisation procedure within 8 weeks after randomisation or 30 days whichever was the longest) (60/224, 27%) than those who had bypass surgery as a first completed revascularisation procedure during the first 8 weeks after randomisation (14/185, 7.0%, $p < 0.001$, chi-squared test). In 42/60 (70%) patients, a failed first attempt at balloon angioplasty was followed by a further intervention and in 39/42 (93%) cases that was surgery (37 bypass surgery).

Those patients who had successful and unsuccessful first attempted balloon angioplasty could not be distinguished by the predictive baseline characteristics (see Chapter 4).

Immediate outcomes by treatment received

Those who had angioplasty as their first intervention were more likely to suffer a primary or secondary failure (60/222, 27%) than those who had surgery as a first procedure (11/184, 6.0%, $p < 0.001$, chi-squared test) (Table 24).

In 42/60 (70%) patients, failed angioplasty was followed by a further intervention and in 36/42 (86%) cases this was bypass surgery. Those patients who had successful and those who had unsuccessful angioplasty could not be distinguished by the predictive baseline characteristics; in particular, the below-knee Bollinger angiogram scores and the number of ankle pressures measurable had a similar distribution in the two groups (Table 27).

Subsequent outcomes by treatment received

For the reasons set out above, to describe subsequent outcomes by treatment received we have chosen to divide the BASIL patient cohort into five groups based upon the nature of the interventions performed during the first 8 weeks after randomisation; namely:

- group 1: successful surgery only in first 8 weeks (n = 173)
- group 2: successful angioplasty only in first 8 weeks (n = 162)
- group 3: unsuccessful surgery (technical failure or further intervention within 8 weeks) (n = 11)
- group 4: unsuccessful angioplasty (technical failure or further intervention within 8 weeks) (n = 60)
- group 5: no intervention in first 8 weeks (n = 46).

TABLE 25 *Reasons why patients randomised to bypass surgery did not undergo surgery as their first procedure*

Reason	*n*
Died/myocardial infarction/deteriorating gangrene	9
Deemed unsuitable for and/or unable to tolerate the procedure	9
Refused intervention	9
Not known	20
Total	47

For group 1 we have further considered outcomes by whether vein (group 1a, n = 132) or prosthetic material (group 1b, n = 41) was used as the conduit.

For group 2 we have further considered outcomes by whether the transluminal (group 2a, n = 87) or subintimal (group 2b, n = 75) route was used (as recorded at the time by the responsible interventionalist).

Bypass surgery groups (1 and 3)

Four patients in group 1 and one patient in group 3 underwent endarterectomy and vein patch rather than bypass surgery (n = 179). Details of the bypass surgery in group 1 (n = 169) and group 3 (n = 10) are given in Table 28. Most bypass surgeries originated at the common femoral artery although 40 (22%) commenced at the level of the knee. With regard to the distal anastomosis, grafts were divided approximately equally between the above-knee popliteal, below-knee popliteal and crural arteries. With regard to the 56 crural artery bypass surgeries, 14 were to the posterior tibial, 20 to the anterior tibial, 18 to the peroneal artery, 14 were proximal third, 16 were middle third and 22 were distal third. There were three dorsalis pedis grafts, one of which involved a 'stop-over' anastomosis to the below-knee popliteal artery. About one-quarter of the grafts involved the use of prosthetic material either wholly or as a composite graft, with or without a vein cuff. Of the vein bypass surgery, over 90% were fashioned predominantly with ipsilateral great saphenous vein (see Chapter 2). As the number of unsuccessful bypass procedures is small it is not possible to make any meaningful comparison between those bypasses that were successful and those that were not.

Balloon angioplasty groups (2 and 4)

Describing often complex attempts at balloon angioplasty for severe multilevel disease is more difficult than describing bypass surgery. We have chosen to describe the balloon angioplasty in groups 2 and 4 by number of disease lengths treated (a disease length may extend across several anatomic arterial segments) and the number of anatomic arterial segments treated. With regard to the former, although in the majority of patients (159/224, 72%) interventionalists reported that they had attempted to treat a single length of disease, in a substantial number of patients it was reported that attempts had been made to treat more than one (up to four) separate disease lengths (Table 29). The numbers of reported transluminal (n = 92) and subintimal (n = 105) balloon angioplasty procedures were approximately equal with just over 10% being reported as mixed.

TABLE 26 *Comparison of patients randomised to surgery who did and did not receive surgery as their first intervention in terms of five baseline variables found to be predictive of overall survival*

	Number of patients					
	As randomised		Not as randomised			
Baseline variable	***n***	**%**	***n***	**%**	**Total**	***p*-value**
All	181		47		228	
Age at randomisation						
Under 70 years	68	85.0	12	15.0	80	0.074[a]
70–79 years	71	79.8	18	20.2	89	
≥ 80 years	42	71.2	17	28.8	59	
Below-knee Bollinger angiography score						
0–4	57	81.4	13	18.6	70	0.87[a]
5–7	56	77.8	16	22.2	72	
≥ 8	55	80.9	13	19.1	68	
Tissue loss						
No tissue loss	47	77.0	14	23.0	61	0.59[b]
Tissue loss	134	80.2	33	19.8	167	
Creatinine						
Low (< 88)	60	75.0	20	25.0	80	0.08[b]
Medium (88–115)	55	77.5	16	22.5	71	
High (> 115)	63	88.7	8	11.3	71	
Number of ankle pressure measurements obtained						
0	24	77.4	7	22.6	31	0.81[a]
1	64	76.2	20	23.8	84	
2	79	85.9	13	14.1	92	
3	14	66.7	7	33.3	21	

a Mantel–Haenzel test for trend.
b Chi-squared test.

The pattern and extent of anatomic segments treated was also complex (Table 30). As expected, the majority of patients underwent treatment of the superficial femoral artery (n = 177) either alone (n = 68) or in combination with the popliteal artery (n = 74) and crural arteries (n = 35). 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. Despite the larger number of unsuccessful balloon angioplasties, as with the surgery groups, it does not appear possible to distinguish successful and unsuccessful procedures in terms of the numbers of disease lengths treated, the type of balloon angioplasty or the anatomic segments treated. Table 31 shows the subsequent treatments undertaken by the patients with failed primary procedures (groups 3 and 4).

Survival curves for these five groups are shown in Figure 15. AFS (p = 0.003, log rank test) but not OS is significantly worse in those patients who have a failed angioplasty (group 4) compared with those having an initially successful (group 2) angioplasty. Neither AFS nor OS is significantly worse after failed surgery (group 3 versus group 1); however, with only 11 failed cases, this comparison has very low power. There are few differences between the other groups and none are significant. Those with no interventions in the first 8 weeks have slightly poorer AFS and OS initially but their long-term survival is somewhat better than the groups treated successfully.

TABLE 27 *Comparison of baseline variables in patients having angioplasty as their first intervention according to whether the procedure was successful (immediate technical success and no further interventions were carried out within the first 8 weeks)*

	Number of patients					
	Technical success and no further major intervention in first 8 weeks		Technical failure or further major intervention in first 8 weeks			
Baseline variable	***n***	**%**	***n***	**%**	**Total**	***p*-value**
All	162	73.0	60	27.0	222	
Age at randomisation						
Under 70 years	43	69.4	19	30.6	62	0.58[a]
70–79 years	80	76.2	25	23.8	105	
≥ 80 years	39	70.9	16	29.1	55	
Below-knee Bollinger angiography score						
1.0 to < 5	51	73.9	18	26.1	69	0.62[a]
2.5 to < 8	50	75.8	16	24.2	66	
≥ 8	51	71.8	20	28.2	71	
Tissue loss						
No tissue loss	36	75.0	12	25.0	48	0.72[b]
Tissue loss	126	72.4	48	27.6	174	
Creatinine						
Low (< 88)	55	77.5	16	22.5	71	0.44[b]
Medium (88–115)	49	69.0	22	31.0	71	
High (> 115)	53	76.8	16	23.2	69	
Number of ankle pressure measurements obtained						
0	30	69.8	13	30.2	43	0.53[a]
1	54	74.0	19	26.0	73	
2	64	71.9	25	28.1	89	
3	14	82.4	3	17.6	17	

a Mantel–Haenzel test for trend.
b Chi-squared test.

Vein versus prosthetic bypass surgery

For group 1 we further considered outcomes by whether vein (group 1a, n = 127) or prosthetic material (group 1b, n = 42) was used as the conduit for bypass surgery. Patients receiving successful vein bypass as their first and only treatment in the first 8 weeks after randomisation (group 1a) had a better outcome in terms of AFS (p = 0.003, log-rank test). but not OS (p = 0.38, log-rank tests) than those receiving successful prosthetic bypasses as their first and only treatment in the first 8 weeks (group 1b) (Figure 16). There was no significant association between the use of prosthetic material for bypass and any of the baseline clinical data (see Chapter 4).

Subintimal versus transluminal balloon angioplasty

For group 2 we have further considered outcomes by whether the transluminal (group 2a, n = 87) or subintimal (group 2b, n = 75) route was used for the first segment treated (as recorded at the time by the responsible interventionalist) for balloon angioplasty. There were no differences in terms of AFS and OS, respectively, between transluminal and subintimal angioplasty (Figure 17).

TABLE 28 *Anatomic extent and type of bypass surgery in 179 patients undergoing a completed bypass surgery as their first attempted revascularisation in the first 8 weeks after randomisation (treatment groups 1 and 3)*

	Group 1: Successful bypass only (*n* = 169)	Group 3: Unsuccessful bypass[a] only (*n* = 10)	All bypasses (*n* = 179)
Proximal anastomosis			
Common femoral artery	120	8	128
Superficial femoral artery	2	0	2
Above-knee popliteal artery	36	0	36
Below-knee popliteal artery	3	0	3
Previous graft	5	1	6
Tibioperoneal trunk	1	0	1
External iliac artery	2	0	2
Data not available	4	1	5
Distal anastomosis			
Above-knee popliteal artery	58	2	60
Below-knee popliteal artery	61	2	63
Posterior tibial artery (proximal third)	2	0	2
Posterior tibial artery (middle third)	3	0	3
Posterior tibial artery (distal third)	8	1	9
Anterior tibial artery (proximal third)	5	1	6
Anterior tibial artery (middle third)	5	1	6
Anterior tibial artery (distal third)	7	1	8
Peroneal artery (proximal third)	5	1	6
Peroneal artery (middle third)	7	0	7
Peroneal artery (distal third)	4	1	5
Dorsalis pedis	2	0	2
Tibioperoneal trunk	1	0	1
Dual popliteal and pedal bypass	1	0	1
Conduit type			
Vein	127	9	136
Prosthetic with vein cuff[b]	28	1	29
Prosthetic with no vein cuff[b]	24	0	24

a Unsuccessful bypass means immediate technical failure or further intervention within 8 weeks of randomisation or 30 days, whichever was longer.
b Prosthetic grafts include composite grafts.

Outcomes of bypass after failed angioplasty

The 37 patients in group 4 who underwent bypass surgery after first attempted failed angioplasty had a poorer AFS (p = 0.006, log rank test) and a somewhat poorer OS (p = 0.06, log rank test) than the 184 patients in groups 1 and 3 who underwent bypass surgery as their first treatment (Figure 18).

Discussion and conclusions

The aim of the BASIL trial was to determine whether for patients with SLI due to infrainguinal arterial disease who are suitable for both bypass surgery and balloon angioplasty, a bypass-surgery-first or a balloon-angioplasty-first strategy is associated with a better outcome in terms of major

TABLE 29 *Number of disease lengths treated and type of balloon angioplasty in 222 patients undergoing attempted balloon angioplasty as their first attempted revascularisation in the first 8 weeks after randomisation (treatment groups 2 and 4)*

	Group 2: Successful angioplasty only (*n* = 162)	Group 4: Unsuccessful angioplasty[a] (*n* = 60)
Number of disease lengths treated		
1	115 (71%)	44 (73%)
2	26 (16%)	14 (24%)
3	19 (12%)	2 (3%)
4	2 (1%)	–
Type of balloon angioplasty attempted		
Transluminal	70 (43%)	22 (37%)
Subintimal	74 (46%)	31 (52%)
Mixed	18 (11%)	7 (11%)

a Unsuccessful balloon angioplasty indicates immediate technical failure or further intervention within 8 weeks of randomisation or 30 days, whichever was longer.

(defined as transtibial or above) AFS and OS, HRQoL and use of hospital resources.

The analysis of the whole cohort by intention to treat showed very little difference in the OS of the whole cohort to either 'amputation or death' or 'death'. However, the hazard for death changed significantly over time ($p < 0.02$ for test of proportional hazards) being non-significantly higher for bypass surgery in the early follow-up (up to 2 years), but then significantly higher for balloon angioplasty after 2 years from randomisation.

The clinically important result is that those patients who survive 2 years and who were initially randomised to surgery gain a significant c. 7 months of additional life (95% CI 1 month to 13 months) and an additional non-significant c. 6 months of amputation-free life (95% CI 0 months to 12 months) over the subsequent follow-up from 2 years to 7 years 9 months from randomisation when compared with those initially randomised to angioplasty (see Chapters 2 and 3).

'By-treatment-received' analyses of randomised trial data must be undertaken and interpreted with great caution (see Chapter 10). However, such analyses of the BASIL trial have been widely requested by clinical colleagues and, if conducted appropriately, can provide useful new insights into the relative merits of the treatments being compared and suggest further areas for research.

Although the great majority of the patients randomised in BASIL underwent an attempt at their allocated treatment fairly quickly after randomisation (see Chapter 2), as was to be expected:

- some of those interventions were significantly delayed
- some of the first procedures were failures (either an immediate technical failure as judged by the responsible surgeon or interventionalist or a delayed clinical failure)
- some patients received the opposite intervention first.

The rate of early secondary procedures was also quite high. Specifically, those assigned to angioplasty were more likely to have a failed procedure whereas those assigned to surgery were more likely to have the opposite or no intervention (see Chapter 2). This was usually because the patient had died, deteriorated, improved or had refused intervention.

Interestingly, overall, those patients treated in the first week after randomisation had a poorer outcome in terms of AFS than those treated in weeks 2–8; despite having a somewhat better predicted prognosis (see Chapter 4). However, it is very important not to overinterpret these life-table analyses because they are based on relatively small numbers of non-randomised, selected patients.

Overall, about one-quarter of the bypass grafts undertaken in the BASIL trial were constructed with prosthetic material. It is widely recognised that

TABLE 30 *Anatomic segments treated in 222 patients undergoing attempted balloon angioplasty as their first attempted revascularisation in the first 8 weeks after randomisation (treatment groups 2 and 4)*

Anatomic segments treated	Group 2: Successful angioplasty (*n* = 162)	Group 4: Unsuccessful angioplasty (*n* = 60)	Total
SFA ± distal segments			
SFA only	49	19	68
SFA + AKPA	44	14	58
SFA + AKPA + BKPA	14	2	16
SFA + AKPA + BKPA+ trifurcation	1	2	3
SFA + AKPA + BKPA + CA unspecified	12	3	15
SFA + AKPA + BKPA+ PerA	0	3	3
SFA + AKPA + BKPA + ATA + PTA	9	3	12
SFA + AKPA + BKPA + ATA + PTA + PerA	1	1	2
Subtotal	130 (80%)	47 (78%)	177
AKPA ± distal segments			
AKPA only	10	5	15
AKPA + BKPA	4	2	6
AKPA + BKPA + CA unspecified	2	1	3
AKPA + BKPA + ATA + PTA	3	0	3
AKPA + BKPA + PerA	1	0	1
AKPA + BKPA + ATA + PTA + PerA	2	0	2
Subtotal	22 (14%)	8 (14%)	30
BKPA ± distal segments			
BKPA only	1	2	3
BKPA + trifurcation	2	0	2
BKPA + CA unspecified	5	3	8
Subtotal	8 (5%)	5 (8%)	13
Crural arteries only			
PerA only	1	0	1
ATA + PTA	1	0	1
Subtotal	2 (1%)	0 (0%)	2
Total	162	60	222

AKPA, above-knee popliteal artery; ATA, anterior tibial artery; BKPA, below-knee popliteal artery; CA, crural artery; PerA, peroneal artery; PTA, posterior tibial artery; SFA,superficial femoral artery.

such grafts are less durable than those fashioned with autogenous vein and it is perhaps not surprising therefore that in BASIL, even when the initially unsuccessful (at 8 weeks) bypass grafts have been excluded from analysis, those constructed with prosthetic material perform significantly worse in terms of AFS, and to a lesser extent OS, than those constructed with vein. Prosthetic bypass also appeared to perform worse than both transluminal and subintimal angioplasty. There was no significant association between the use of prosthetic material, as opposed to vein, for bypass and any of the baseline clinical variables, Bollinger scores, TASC II classification or BASIL randomisation stratification group. So this lack of durability does not appear to be the result of the selection of higher-risk patients for prosthetic use.

Although it is not, strictly speaking, appropriate to compare statistically the 'intention to treat'

TABLE 31 *Further treatments after a failed primary procedure (groups 3 and 4) within the first 8 weeks from randomisation or 30 days after the primary intervention*

Next treatment	Group 3: Unsuccessful bypass surgery (n = 10)	Group 4: Unsuccessful balloon angioplasty (n = 60)	Total
No further treatment	1	12	13
BSX and endarterectomy	0	1	1
BSX	2	37	39
Endarterectomy	0	1	1
BAP	1	7	8
Stent	1	0	1
Chemical sympathectomy	0	1	1
Thromboembolectomy	6	1	7
Total	11	60	71

BAP, balloon angioplasty; BSX, bypass surgery.

and the 'on-treatment' outcomes of those receiving a vein bypass, a prosthetic bypass, or an angioplasty (transluminal or subintimal), it seems reasonable to suggest that the overall BASIL trial recommendation that patients likely to live more than 2 years after intervention should have surgery rather than angioplasty (see Chapter 3) should be viewed in the context of the available bypass conduit.

It seems at least possible that had only those patients able to undergo vein bypass been randomised in BASIL, then the longer-term advantages of surgery over angioplasty in terms of AFS, and possibly OS, would have been substantially greater than those actually observed because of the inclusion of a significant number of generally very poorly-performing prosthetic bypasses in the surgery arm. It also seems likely that those patients who could not undergo a vein bypass would in many cases have been better served by an attempt at angioplasty, where possible, in the first instance (even if their predicted survival was greater than 2 years – see Chapter 4). The BASIL trial data reaffirm once again that surgeons should make every effort to use vein and to view prosthetic material in such patients as a last resort.

It is often said, although on the basis of little real evidence, that an unsuccessful angioplasty does not jeopardise the chances of subsequent bypass surgery. In other words, apart from the cost, there is nothing to lose by at least trying angioplasty first – if it works then all well and good and, if it does not work then proceed to surgery. Notwithstanding all the caveats surrounding 'on-treatment' analyses, the BASIL trial data do not support this 'free shot' view of angioplasty. Those patients randomised to angioplasty and who undergo bypass surgery after failure of that angioplasty do badly in terms of OS, but especially AFS, and significantly worse than those who have been randomised to and undergone bypass surgery. It is not possible to know at this stage whether this is because a failed angioplasty:

- selects out, and is therefore simply a marker for, those with a worse prognosis who were going to do badly whatever treatment they received as their primary treatment, or
- reduces *per se* the chances of successful surgical revascularisation by affecting either the type and extent of bypass required or the run-off from such a bypass.

Further work is ongoing to try to resolve these factors. However, whatever the reasons, a failed angioplasty is certainly associated with a poor outcome.

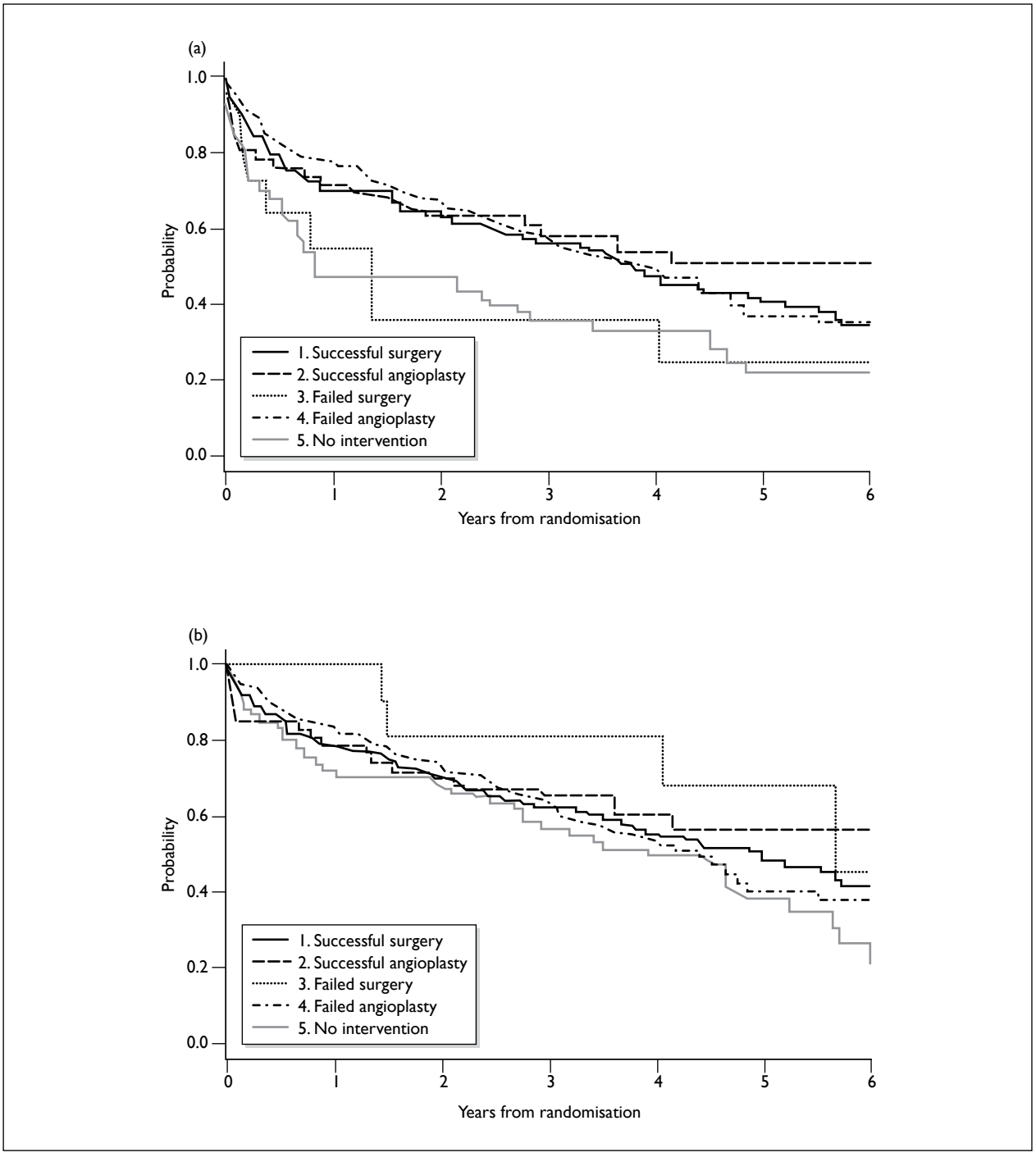


FIGURE 15 *(a) Amputation-free survival and (b) overall survival curves for the five by-treatment groups.*

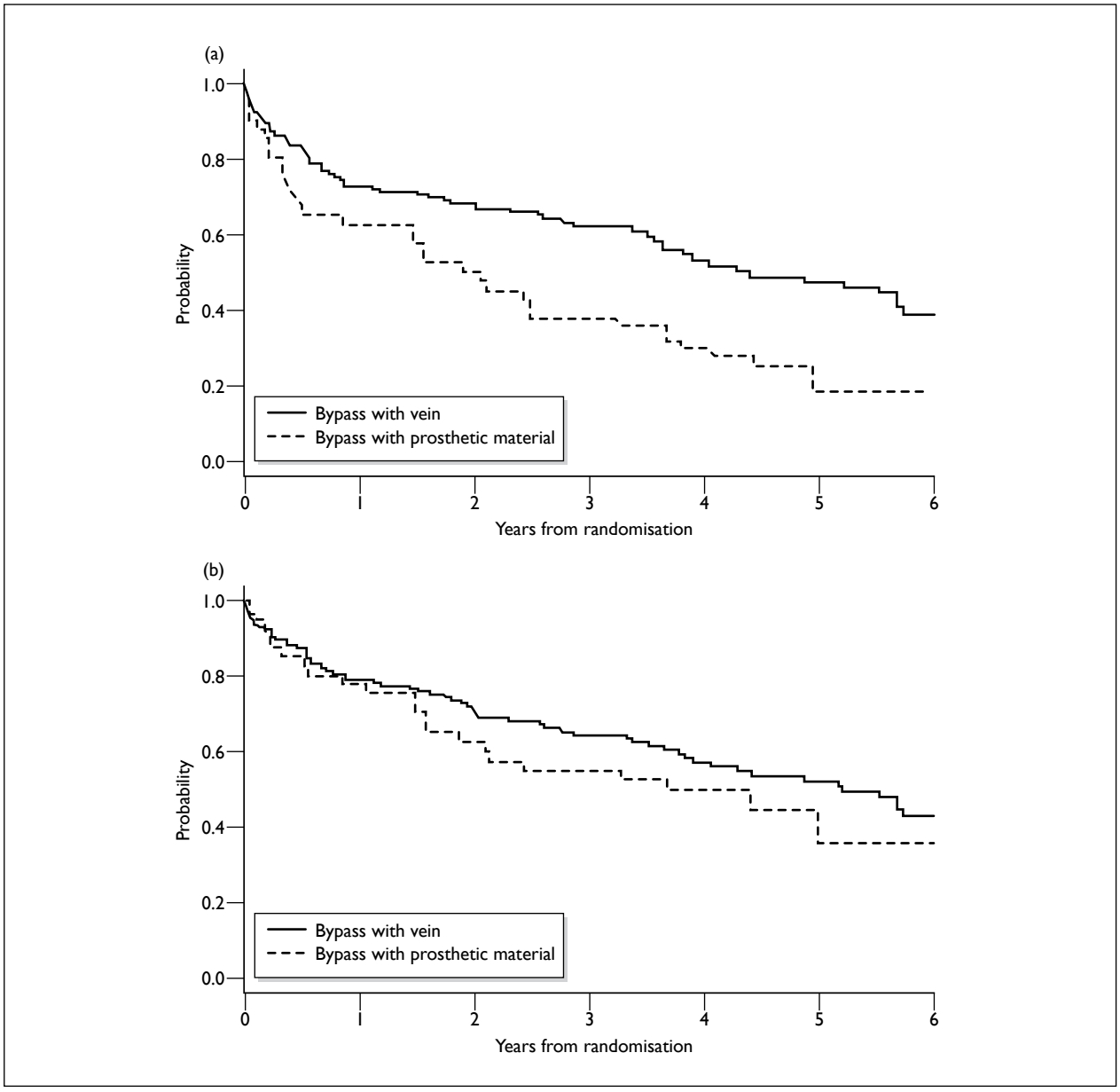


FIGURE 16 *(a) Amputation-free survival and (b) overall survival curves for patients undergoing initially successful surgery (group 1) according to type of bypass conduit.*

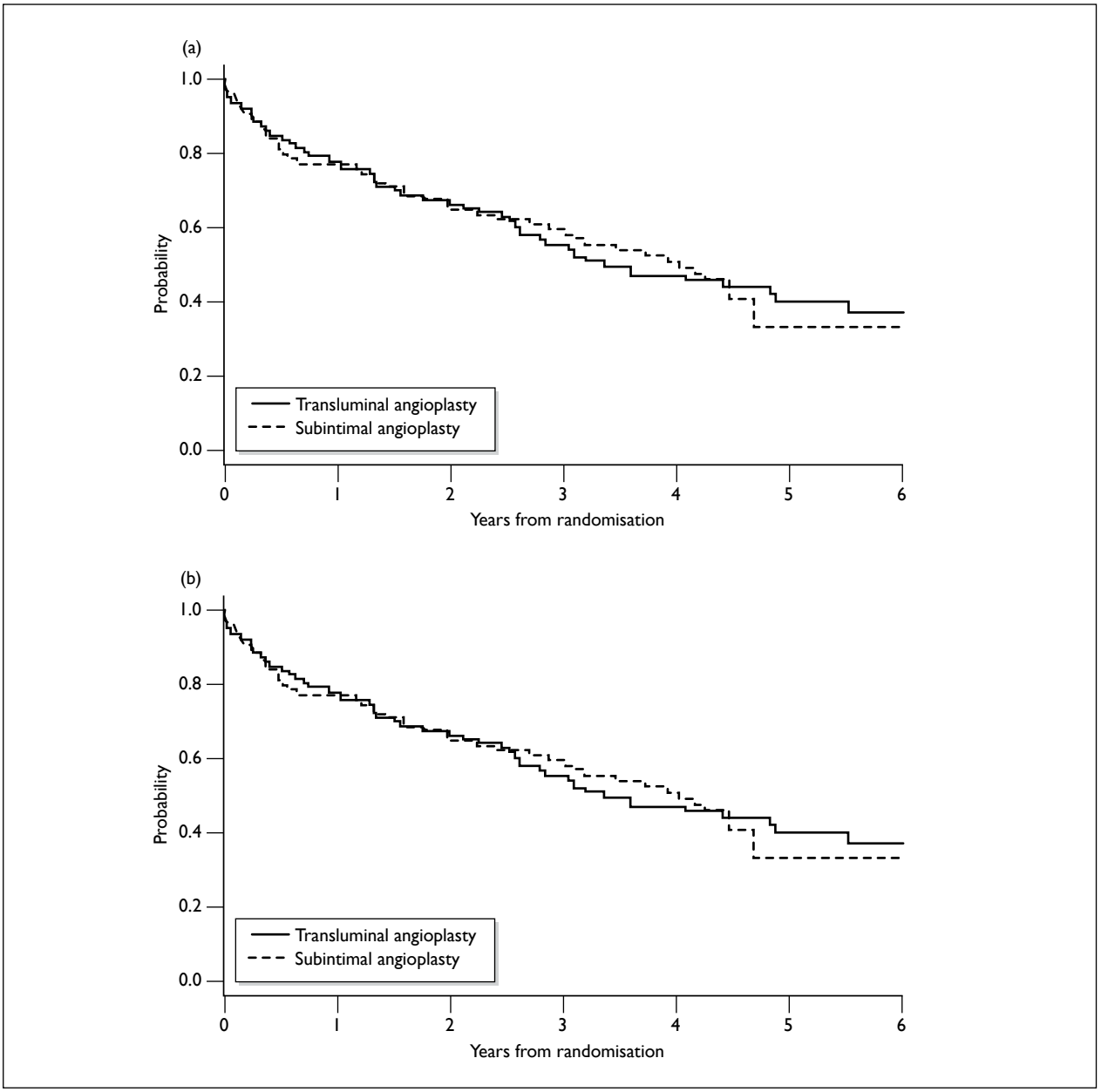


FIGURE 17 *(a) Amputation-free survival and (b) overall survival curves for patients undergoing initially successful angioplasty (group 2) by type (transluminal versus subintimal).*

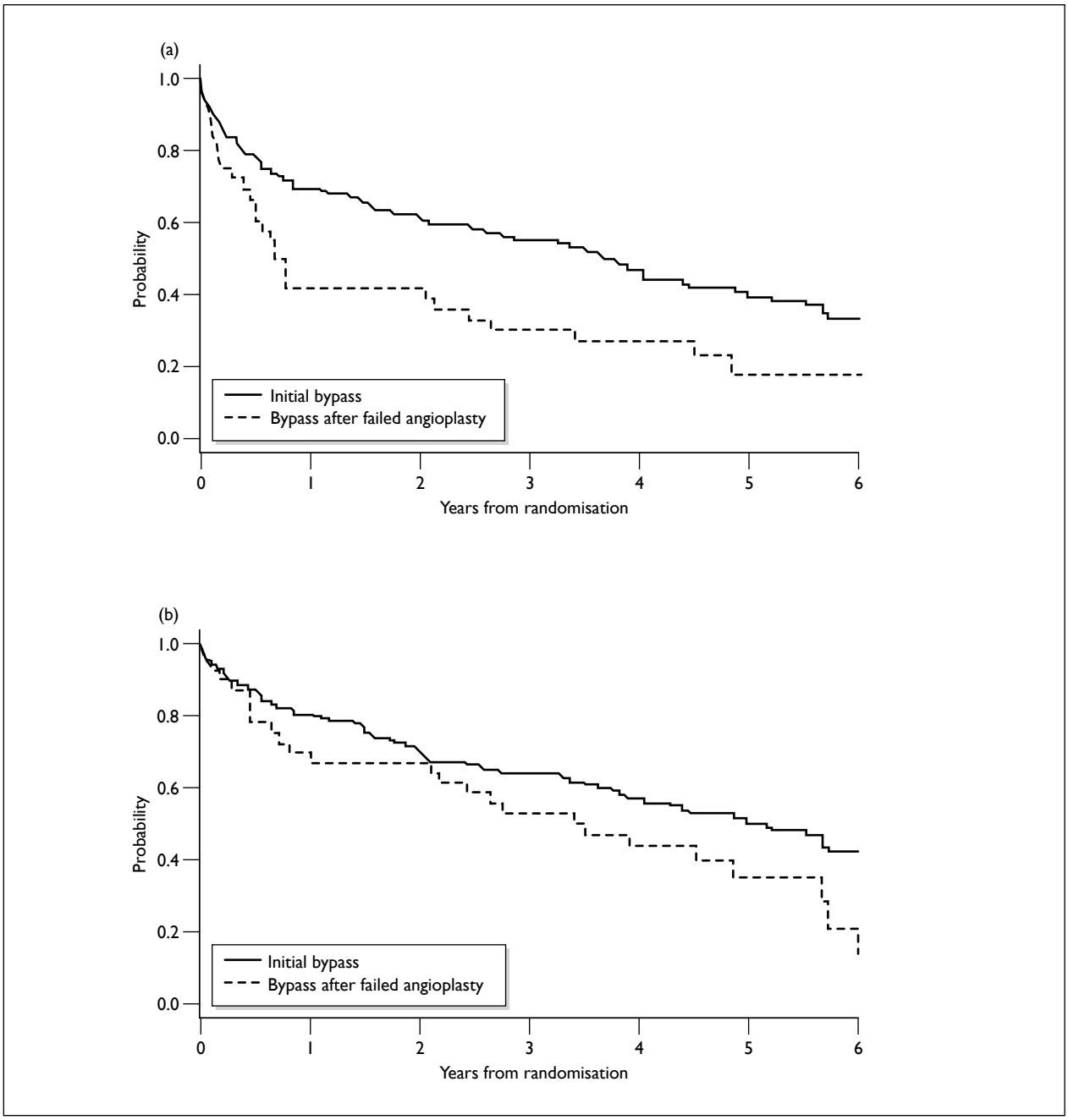


FIGURE 18 *(a) Amputation-free survival and (b) overall survival in patients randomised to and undergoing bypass surgery and patients undergoing bypass surgery after failed angioplasty.*

Chapter 6
Angiogram scoring

Introduction

As stated in the original protocol (see Appendix 1), the BASIL trial investigators and participants believed that it was important for several reasons to be able to describe qualitatively and quantitatively the severity and distribution of disease in patients randomised within the trial:

- to establish that patients in the two arms were comparable in terms of disease severity
- to describe the distribution of disease in the trial patients to permit clinicians to make judgements about the appropriateness of generalising BASIL trial results to other groups of patients affected by and undergoing treatment for SLI
- to derive summary measures that could be used in predicting the outcomes of the trial
- to allow further subgroup analysis based on disease distribution.

To that end all centres were asked to forward copies of preintervention angiograms (or other imaging) for all patients randomised in the trial.

It was decided to use the Bollinger scoring method for this purpose. Although it is detailed in its description of both the severity and extent of disease, it is user-friendly and of all the various disease-severity scoring methods that have been devised, it has probably been used most widely. We also scored the angiograms according to the TASC II classification (this was not specified in the trial protocol as it was not in existence when the trial was designed).

Methods

Preintervention angiograms of the trial leg were scored according to the Bollinger method[52] (Table 32) by two consultant vascular interventional radiologists, Dr K McBride and Dr R Ashleigh, unaware of the treatment received or outcome. Each made an independent assessment of 13 infrainguinal segments:

- profunda femoris (PFA)
- proximal and distal superficial femoral (Pr-SFA, Di-SFA)
- proximal (above-knee) and distal (below-knee) popliteal artery (Pr-PA, Di-PA)
- tibioperoneal trunk (TPT)
- proximal (upper half calf) and distal (lower half calf) posterior tibial (Pr-PT, Di-PT)
- proximal and distal anterior tibial (Pr-AT, Di-AT)
- proximal and distal peroneal (Pr-Per, Di-Per), and plantar arch.

Each of these segments was scored according the severity and extent of disease (Table 32).

Four severities of lesion are characterised in the Bollinger method:

TABLE 32 *Bollinger scoring system*[a]

Severity				
Occlusion	**Stenosis > 50%**	**Stenosis < 50%**	**Plaques < 25%**	**Extent**
	4	2	1	Single lesion
13	5	3	2	Multiple lesions affecting less than half the segment
15	6	4	3	Multiple lesions affecting more than half the segment

a The vertical columns represent the different severities of atherosclerotic lesion observed and the rows represent the extent of the disease observed in each segment. The additive score for each segment is the score in the first column where there are occlusions.

- complete occlusion of the lumen
- stenosis > 50% of the luminal diameter
- stenosis < 50% but > 25% of the luminal diameter
- plaques impinging on < 25% of the diameter.

Each type of lesion is further categorised as follows by its extent, namely:

- single lesion
- multiple lesions affecting less than half of the segment
- multiple lesions affecting more than half of the segment.

To calculate the summary scores, the individual scores for each of the three lesion severities are summed in accordance with the following rules:

- in the presence of occlusions, stenoses and plaques are not considered
- when both severities of stenoses are present (< 50% and > 50%), plaques (< 25%) are not considered
- for each severity of disease only one extent of disease category is scored.

The plantar arch (where it was included on the angiograms) was scored as either present or absent.

Not all segments could be scored on all angiograms; in particular, despite being requested, foot views were often not available or were of insufficient quality to allow full scoring of the forefoot plantar arch.

An analysis comparing the two observers revealed a small bias between the scores and some cases where there were substantial differences between the two (full data available on request).

Those angiograms where the difference in the total scores for the 13 segments between the two observers exceeded 25 (73 cases) were scored by a panel comprising a further consultant vascular interventional radiologist (Dr I Gillespie) and two consultant vascular surgeons (Mr D Adam and Professor A Bradbury) who scored the angiograms blind to the scores of the first two observers and the patient's treatment and outcome. This panel was found to be in better agreement with observer 1 than observer 2.

A final score for each of the 13 segments was obtained by taking:

- the panel score when that was available
- the score from the 'better' (defined as being closer to the panel score) observer 1 where this segment had not been scored
- the score from observer 2 in the relatively few cases where observer 1 was missing.

This process substantially reduced the proportion of missing data at all sites except the plantar arch where, as noted above, angiograms did not include the forefoot in a substantial number of patients.

For the remaining 12 segments only 1.2% of segments were missing.

For the TASC II assessment, angiograms were classified into A (least severe), B, C and D (most severe) by a single vascular surgeon, Professor A Bradbury, who was unaware of the treatment received and the outcome (Figure 19).

Results

Summary of scores by segment

The distribution of disease at each arterial segment is given in Table 33 and shown graphically, without the plantar arch data, in Figure 20. We can see that the greatest burden of disease is in the tibial arteries and in the segments above the knee.

Table 34 shows the number of sites scored per patient, excluding the plantar arch. Very few patients have anything other than complete data. The mean score was therefore computed by taking the mean of all available data for each patient, equivalent to imputing the missing values by the mean of the other segments for this patient.

Comparison of disease in the two treatment arms

Mean scores for the above-knee and below-knee segments, and for each individual segment (excluding the plantar arch) by randomised group are shown in Table 35. As to be expected from the randomisation process, the two groups were very well matched on individual segment and overall mean scores. All further analysis is therefore presented for the trial cohort as a whole.

Analysis of patterns of disease in the trial cohort as a whole

Exploratory analyses were carried out to further understand the pattern of disease in these patients.

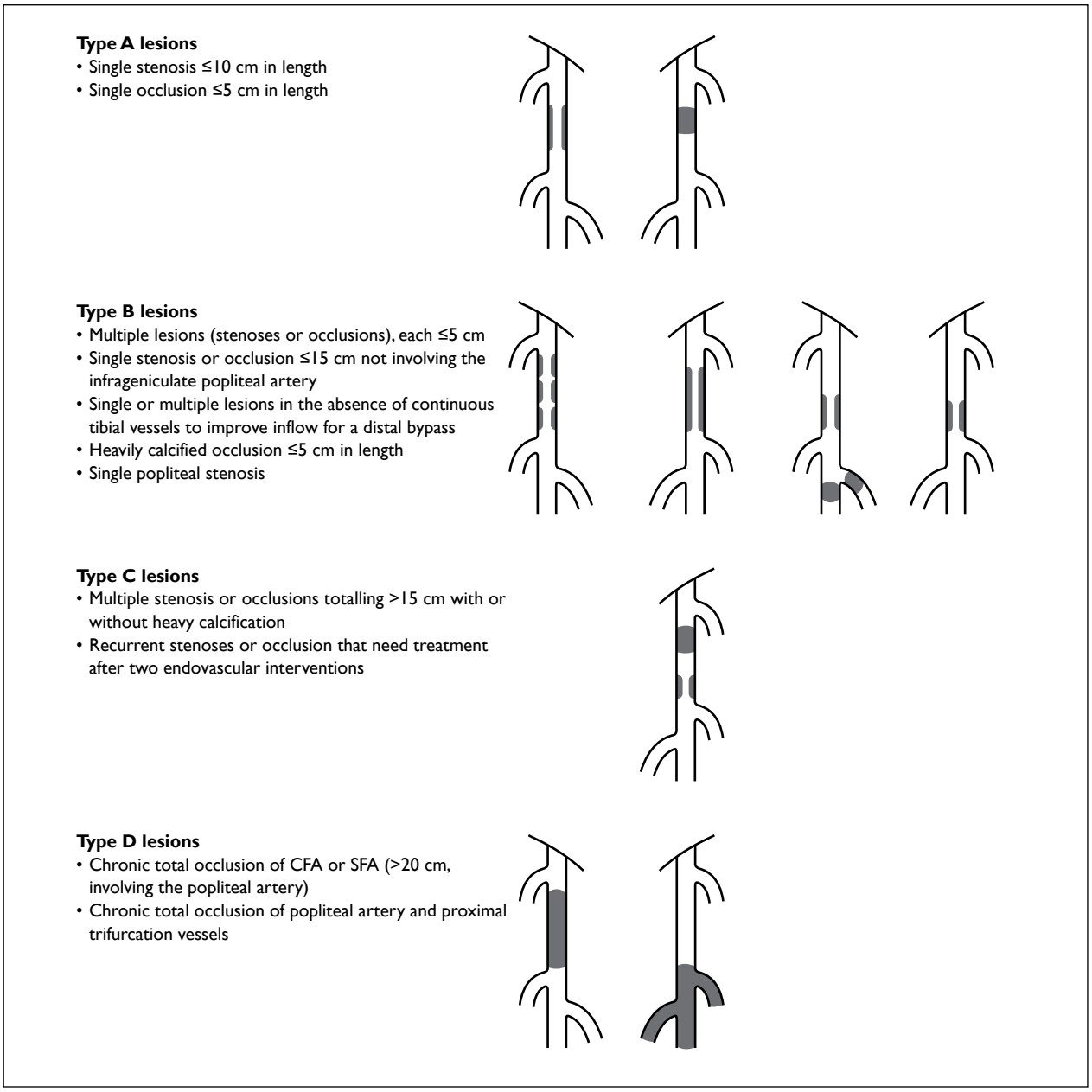


FIGURE 19 *TASC II classification.*

The data were divided into five approximately equal-sized groups (83, 87, 84, 80, 84 – uneven numbers due to ties) according to their mean overall score from 1 (best) to 5 (worst). Figure 21 shows the mean score at each of the segments for the five groups.

We can see that all the groups have disease in the upper segments, while the lower segments are progressively more affected in those groups with higher mean scores. The central segments only become affected in the most severe groups. Patients with the least overall disease tend to have their disease concentrated in the SFA and popliteal artery which were the commonest sites of disease overall. As the overall severity of disease increases, the crural arteries become increasingly involved in addition to the more proximal disease. The posterior tibial was the worst affected crural artery while the peroneal appears relatively spared.

Correlations between disease burdens in the 13 different arterial segments are shown in Table 36.

The strongest relationships are between disease in the:

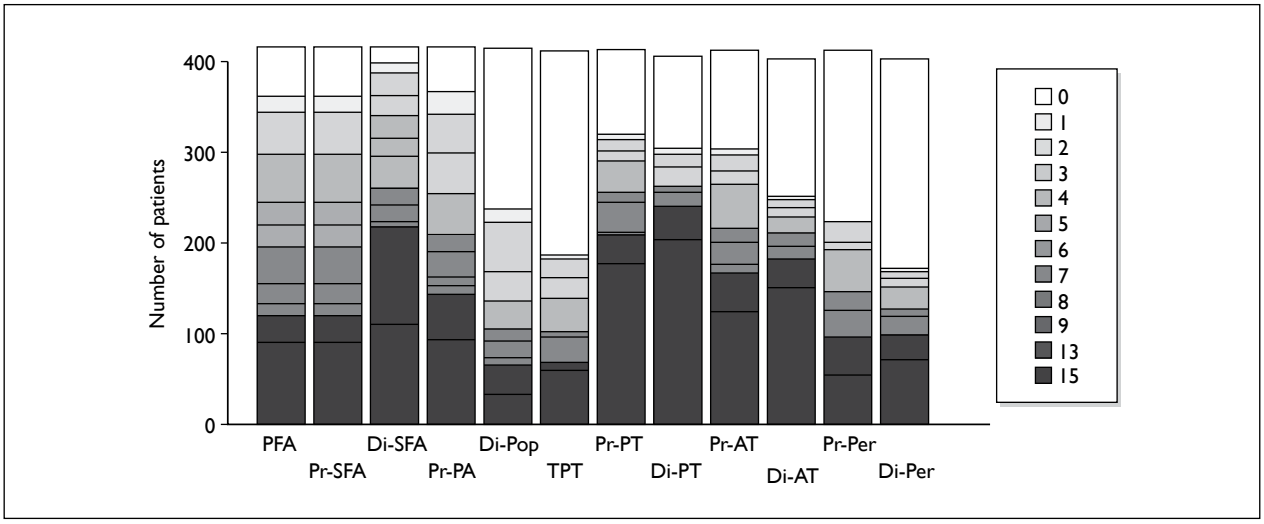


FIGURE 20 *Distribution of Bollinger scores (0 to 15) in each arterial segment (plantar arch excluded). The proportions of each segment occluded are shown with the heaviest shading at the bottom of each bar, partially affected segments have intermediate shading and the proportions unaffected in each bar are shown 'unshaded' at the top of each bar. PFA, profunda femoris; Pr-SFA, Di-SFA, proximal and distal superficial femoral; Pr-PA, Di-PA, proximal (above-knee) and distal (below-knee) popliteal; TPT, tibioperoneal trunk; Pr-PT, Di-PT, proximal (upper half calf) and distal (lower half calf) posterior tibial; Pr-AT, Di-AT, proximal and distal anterior tibial; Pr-Per, Di-Per, proximal and distal peroneal.*

- proximal and distal SFA
- distal popliteal and tibioperoneal trunk
- tibioperoneal trunk and proximal PT and peroneal
- proximal and distal halves of the three crural vessels (PT, AT, peroneal).

There are also some interesting negative correlations. Specifically, it appears that significant disease is often present in the SFA or the popliteal/TPT segment but not both. This probably reflects the fact that to be randomised in BASIL the patients had to be treatable by both surgery and

TABLE 33 *Severity and distribution of arterial disease in the trial cohort as a whole as quantified by the Bollinger scoring method*

Arterial segment	Percentage of patients by Bollinger scores for each individual arterial segment												*n*
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**13**	**15**	
Profunda	44.4	9.7	15.9	4.6	9.4	3.9	4.6	0.7	0.2	0.2	3.6	2.7	414
Proximal SFA	13.4	4.1	11.3	12.7	5.8	6.0	9.6	5.5	3.1	0.2	6.7	21.6	417
Distal SFA	4.1	2.6	6.2	5.0	6.5	4.6	8.9	4.1	4.6	1.0	26.1	26.4	417
Proximal popliteal	11.8	6.0	10.3	10.8	10.6	4.8	6.7	2.4	1.9	0.2	12.0	22.5	417
Distal popliteal	42.5	3.6	13.0	7.9	7.5	3.1	4.8	1.4	0.5	–	7.2	8.4	416
Tibioperoneal	54.7	1.0	5.1	5.3	9.0	1.2	7.0	–	0.2	–	1.9	14.5	413
Proximal PT	22.5	1.4	3.1	2.7	8.5	2.4	8.0	0.7	–	–	7.7	43.0	414
Distal PT	24.8	0.2	1.7	3.2	5.2	2.0	2.9	0.2	0.2	0.2	8.6	50.6	407
Proximal AT	26.6	1.4	4.3	3.4	11.6	3.9	5.8	1.9	0.2	–	10.6	30.2	414
Distal AT	37.6	0.7	2.2	2.2	4.5	3.7	3.2	0.2	0.2	–	7.7	37.6	404
Proximal peroneal	45.4	0.7	4.8	1.9	11.4	4.8	7.2	–	–	–	9.9	13.8	414
Distal peroneal	57.0	0.5	2.0	2.7	5.9	2.0	4.9	–	–	–	6.4	18.5	405
Plantar arch	12.1	–	–	–	14.1	–	54.4	–	–	–	–	19.4	340

AT, anterior tibial; PT, posterior tibial; SFA, superficial femoral artery.

TABLE 34 *Numbers of sites scored for each patient excluding the plantar arch*

Number of segments scored per patient[a]	12	11	10	9	8	5	4
Number (%) of patients in whom that number of segments was scored	399 (95.45)	3 (0.72)	3 (0.72)	9 (2.15)	2 (0.48)	1 (0.24)	1 (0.24)
Segments scored	768	33	30	18	16	5	4
Cumulative %	95.45	96.17	96.89	99.04	99.52	99.76	100

a Excludes plantar arch.

angioplasty. Patients with very extensive disease would have been untreatable or only treatable by bypass.

It therefore appears that to be considered treatable by angioplasty, interventional radiologists required most of the BASIL patients randomised to have a re-entry point, usually around the level of the knee. This is further shown in Tables 37 and 38.

Above-knee and below-knee Bollinger scores and outcomes

These exploratory analyses suggest that, in the analysis of the outcomes of the trial we should consider separately the mean Bollinger scores for arterial segments above and below the knee (excluding the plantar arch). The contribution these mean scores make to predicting outcome is presented in Chapter 4.

Relationship between Bollinger score and TASC II scores

TASC II scores were available for 411 of the 418 patients with Bollinger scoring. The relationship between increasing burden of disease on Bollinger scoring, TASC II score and BASIL stratification group at randomisation (see Chapter 2) is shown in Table 39. As expected, trial patients are predominantly in the higher TASC II groups, with very few in group A.

TABLE 35 *Comparison of Bollinger scores by randomised groups*

	Angioplasty (A)			Bypass (B)			
Mean Bollinger score	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**Difference A–B**
Mean score	208	6.19	2.23	210	6.23	2.22	–0.04
Profunda	208	2.53	3.82	206	2.18	3.23	0.35
Proximal SFA	208	6.77	5.44	209	6.27	5.49	0.50
Distal SFA	207	9.64	5.14	210	9.19	5.21	0.46
Proximal popliteal	207	6.90	5.65	210	6.98	5.72	–0.08
Distal popliteal	207	3.86	5.00	209	3.37	4.82	0.50
Tibioperoneal	207	3.61	5.44	206	3.51	5.23	0.09
Proximal PT	207	8.65	6.54	207	8.55	6.36	0.10
Distal PT	207	9.29	6.67	200	9.49	6.56	–0.20
Proximal AT	207	7.14	6.24	207	7.40	6.36	–0.26
Distal AT	206	7.18	6.81	198	7.54	6.92	–0.36
Proximal peroneal	207	4.49	5.71	207	4.80	5.65	–0.31
Distal peroneal	206	3.99	5.99	210	4.76	6.18	–0.77
Above-knee score	208	6.47		210	6.17		0.29
Below-knee score[a]	208	6.02		210	6.14		–0.13

AT, anterior tibial; PT, posterior tibial; SFA, superficial femoral artery.
a Excludes plantar arch.

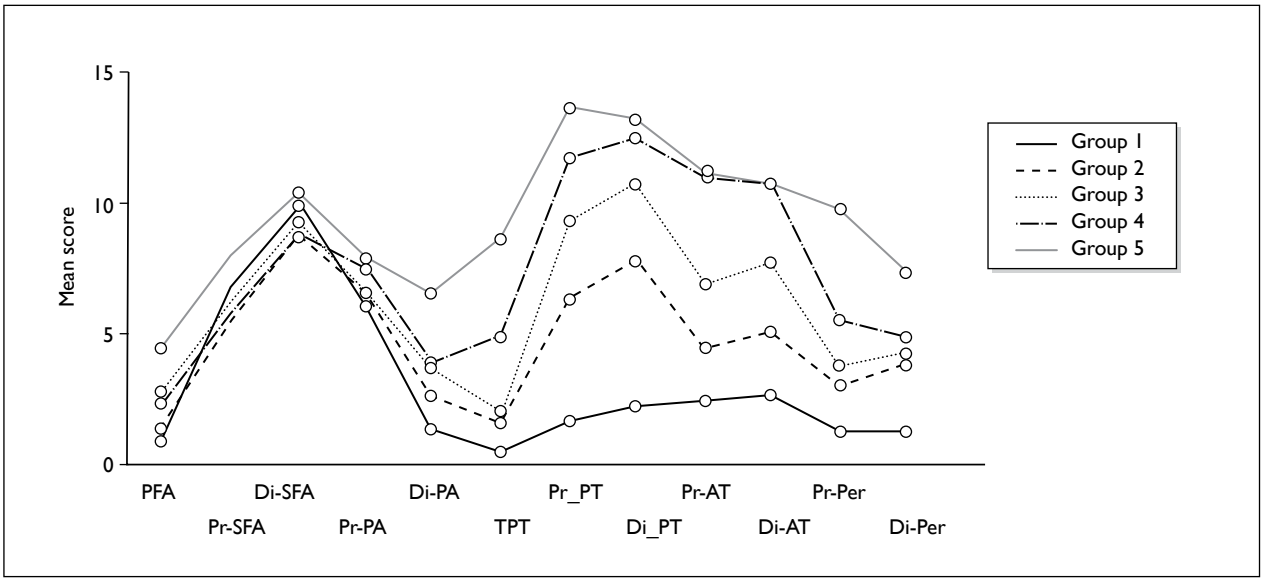


FIGURE 21 *Pattern of disease in five approximately equal-sized groups according to mean overall Bollinger score, where group 1 is least overall disease and group 5 is worst overall disease. Profunda femoris (PFA); proximal and distal superficial femoral (Pr-SFA, Di-SFA); proximal (above-knee) and distal (below-knee) popliteal (Pr-PA, Di-PA); tibioperoneal trunk (TPT); proximal (upper half calf) and distal (lower half calf) posterior tibial (Pr-PT, Di-PT); proximal and distal anterior tibial (Pr-AT, Di-AT); proximal and distal peroneal (Pr-Per, Di-Per).*

TABLE 36 *Correlations (× 100) between individual patients' Bollinger scores at different arterial segments*

	Profunda	Proximal SFA	Distal SFA	Proximal popliteal	Distal popliteal	Tibioperoneal	Proximal PT	Distal PT	Proximal AT	Distal AT	Proximal peroneal	Distal peroneal	Plantar arch
Profunda		11	–1	–6	7	13	15	14	13	11	13	7	6
Proximal SFA	11		57	**–22**	**–31**	**–25**	–9	–4	–7	–3	–13	–4	3
Distal SFA	–1	57		–12	**–28**	**–20**	–16	–14	–9	–10	–16	–5	–11
Proximal popliteal	–6	**–22**	–12		18	–2	2	–3	–1	2	6	–4	–3
Distal popliteal	7	**–31**	**–28**	18		41	25	13	19	5	20	13	–0
Tibioperoneal	13	**–25**	**–20**	–2	41		40	25	19	7	49	23	13
Proximal PT	15	–9	–16	–2	25	40		78	23	11	24	–4	22
Distal PT	14	–4	–14	–3	13	25	78		12	6	14	–4	33
Proximal AT	13	–7	–9	–1	19	19	23	12		73	9	–6	10
Distal AT	11	–3	–10	2	5	7	11	6	73		–0	–7	16
Proximal peroneal	13	–13	–16	–6	20	49	24	14	9	–0		54	13
Distal peroneal	7	–4	–5	–4	13	23	–4	–4	–6	–7	54		4
Plantar arch	6	3	–11	–3	–0	13	22	33	10	16	13	4	

AT, anterior tibial; PT, posterior tibial; SFA, superficial femoral artery.
Dark grey boxes denote correlations that are significantly different from zero ($p < 0.05$); light grey boxes denote when a correlation is negative; figures in bold denote significant negative correlations.

TABLE 37 *Association between disease in the superficial femoral artery and in the popliteal artery and tibioperoneal trunk*

Highest score for superficial femoral artery	Highest score from proximal and distal popliteal and tibioperoneal trunk, *n* (%)			
	No disease	Stenotic disease	Occluded	Total
No disease	1 (10)	0 (0)	9 (90)	10 (2.4)
Stenotic disease	6 (3.4)	62 (35)	109 (61.6)	177 (42.3)
Occluded	24 (10.4)	113 (48.9)	94 (40.7)	231 (55.3)
Total	31 (7.4)	175 (41.9)	212 (50.7)	418 (100)

TABLE 38 *Relationship between occlusion in the peroneal artery and disease in the other crural arteries and more proximal segments*

			Status of proximal arterial segments			
Status of peroneal artery	Which other crural arteries occluded	Number of patients	SFA, popliteal and TPT occluded	SFA occluded	SFA, popliteal and TPT patent	Popliteal and TPT occluded
Patent (*n* = 278, 66.5%)	Neither	70	12	41	6	11
	Only AT	44	9	13	10	12
	Only PT	75	18	23	15	19
	AT and PT	89	20	27	18	24
Occluded (*n* = 140, 33.5%)	Neither	20	4	5	2	9
	Only AT	23	7	7	6	3
	Only PT	44	11	13	7	13
	AT and PT	53	13	8	5	27

AT, anterior tibial; PT, posterior tibial; SFA, superficial femoral artery; TPT, tibioperoneal trunk.

Although the TASC II and Bollinger scores are generally related, there are also many cases where they disagree. Furthermore, there is very little evidence of a relationship between the TASC II score and clinical presentation. In Chapter 4 we show that the Bollinger scores, especially the lower leg mean score, are much more strongly related to the outcomes than is TASC II classification.

Bollinger scores do not relate closely to BASIL trial stratification group either (Table 40).

Discussion and conclusions

Preintervention angiograms were available and of sufficient quality to be scored for 418 of 452 (92.5%) randomised patients and 5229 of 5434 (96.2%) arterial segments. There were no significant differences between the randomised groups in respect of any of the arterial segments.

The strongest relationships are between disease in the proximal and distal SFA, distal popliteal and tibioperoneal trunk, tibioperoneal trunk and proximal PT and peroneal, and between the proximal and distal halves of the three crural vessels (PT, AT, peroneal). There are also some interesting negative correlations. Specifically, it appears that significant disease can be present in the SFA or the popliteal/TPT segment but not often in both. This probably reflects the fact that to be randomised in BASIL the patients had to be treatable by both surgery and angioplasty. Patients with very extensive disease would have been untreatable or only treatable by bypass. By contrast, it appears that in order to be considered treatable by angioplasty, interventional radiologists required most of the BASIL patients randomised to have a re-entry point, usually around the level of the knee.

Patients with the least overall disease tend to have their disease concentrated in the SFA and popliteal artery, which were the commonest sites of disease overall. As the overall severity of disease increases, the crural arteries become increasingly involved in addition to the more proximal disease. The PT was the worst affected crural artery while the peroneal appears relatively spared.

TABLE 39 *The relationship between increasing burden of disease on Bollinger scoring, TASC II classification of disease and BASIL randomisation group*

	Patients separated into five groups by overall burden of disease on Bollinger scoring (1 = least disease to 5= most diseased), *n*					
	1	**2**	**3**	**4**	**5**	**Total**
TASC II classification						
	83 (one missing TASC II)	87	84 (two missing TASC)	80 (two missing TASC)	84 (two missing TASC)	418
A	4	5	2	.	1	12
B	30	28	27	26	11	122
C	42	40	39	26	37	184
D	6	14	14	26	33	93
BASIL randomisation stratification group[a]						
A	14	26	13	13	13	79
C	46	36	50	36	39	207
B and D	23	25	21	31	32	132

a Randomisation was stratified by centre, and then into four groups by clinical presentation (rest pain only vs tissue loss) and ankle pressure (≥ 50 mmHg vs < 50 mmHg); namely (A) rest pain only, ≥ 50 mmHg; (B) rest pain only, < 50 mmHg; (C) tissue loss, ≥ 50 mmHg; and (D) tissue loss < 50 mmHg. As B is a very small group it is combined with D to form a group with ankle pressure < 50 mmHg, which had the poorest outcome of all groups.

TABLE 40 *Bollinger scores and BASIL stratification group*

	BASIL randomisation stratification group[a]			
Bollinger score groupings	**A**	**C**	**B and D**	**All**
All	93	222	137	452
Total score	14	15	5	34
Group 1	14	46	23	83
Group 2	26	36	25	87
Group 3	13	50	21	84
Group 4	13	36	31	80
Group 5	13	39	32	84
Above-knee mean score	14	15	5	34
under 5	28	73	33	134
5 to < 8	30	79	56	165
≥ 8	21	55	43	119
Below-knee mean score	14	15	5	34
< 5	34	77	47	158
5 to < 8	26	68	37	131
≥ 8	19	62	48	129

a Randomisation was stratified by centre, and then into four groups by clinical presentation (rest pain only vs tissue loss) and ankle pressure (≥ 50 mmHg vs < 50 mmHg); namely (A) rest pain only, ≥ 50 mmHg; (B) rest pain only, < 50 mmHg; (C) tissue loss, ≥ 50 mmHg; and (D) tissue loss < 50 mmHg. As B is a very small group it is combined with D to form a group with ankle pressure < 50 mmHg, which had the poorest outcome of all groups.

As might be expected there is general agreement between TASC II, BASIL randomisation group and Bollinger although the level of agreement is quite low and there are many patients where they are not in agreement.

Taken together with the data presented in Chapter 4 it appears that what determines outcome (both AFS and OS) for the BASIL trial patients is the extent and severity of disease below the knee as quantified by:

- the number of recordable ankle pressures (one, two or three crural vessels)
- the mean below-knee Bollinger scores
- the highest recordable ankle pressure.

The TASC II classification which focuses on the femoropopliteal segment is insensitive to these differences. Although useful in managing patients with intermittent claudication at a single level (usually femoropopliteal disease) its utility does not appear to extend to patients with SLI who also have a significant burden of distal disease below the knee.

One of the main criticisms levelled against all RCTs is their lack of generalisability. In Chapter 2 we describe the results of the BASIL trial audit undertaken in the top six recruiting centres. This showed, surprisingly perhaps, that only about 50% of patients presenting to these units with SLI underwent some form of revascularisation. Of those that did, about 30% were randomised within the BASIL trial.

Although the data presented above clearly indicate that the BASIL trial patients had, for the most part, severe and extensive multilevel disease, they are likely to represent the 'good' end of the disease spectrum for this patient group in that they were:

- offered a revascularisation procedure at all
- considered suitable for angioplasty.

As a consequence, although the outcomes for the BASIL trial cohort were extremely poor in terms of AFS, OS and HRQoL (see Chapters 2, 3, 4 and 7) almost regardless of what treatment they received, it is likely that the outcomes for the SLI (or CLI) patient group as a whole will be significantly worse.

However, by presenting the clinical and angiographic severity of disease of the BASIL trial cohort in great detail we believe we are allowing clinicians to assess for themselves with a high degree of accuracy and confidence whether and how the BASIL trial cohort (and its findings) relates to their own SLI patient population, so addressing concerns about generalisability and applicability.

Chapter 7

Health-related quality of life, resource utilisation and cost-effectiveness analyses

Introduction

We have already presented the main clinical outcomes of the study to 2005 (Chapter 2) and to 2008 (Chapter 3). Here we present a more detailed analysis of trial patients' HRQoL before and after intervention, hospital-resource utilisation after intervention and cost-effectiveness.

Methods

Overview

The BASIL trial design integrated measurement of survival, AFS, HRQoL and the use of hospital inpatient services. These trial outcomes allowed consideration of the primary health and resource consequences following different strategies for managing SLI. Individual patient hospital costs were collected to the end of follow-up. All analyses were by intention to treat using the perspective of the individual patient for HRQoL and the hospital sector for resource use.

Health-related quality of life

We measured HRQoL using standard generic and disease-specific measures. Two generic measures, the EQ-5D[42] and the SF-36,[43] were used along with the VascuQoL.[53] For EQ-5D, SF-36 scales/summary scores and VascuQoL, higher scores indicate better health and well-being as perceived by the patient.

These measures were collected using a self-administered protocol at baseline/randomisation and at 3, 6, 12, 24 and 36 months after randomisation. All patients were asked to provide HRQoL data out to 3 years from randomisation whether or not they had undergone major amputation of the trial leg. The HRQoL questionnaires are shown in Appendix 4.

EuroQoL 5D

The $EQ\text{-}5D_{index}$ covers five dimensions: mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Each dimension has three levels (no problem, some problem or extreme problem) and subjects are asked to indicate the level that corresponds to their current level of function or experience on each dimension.

The EQ-5D responses were converted into a single weighted utility (preference-based) score using the original time trade-off tariff set.[44] This is a standard and well-established set of preference weights used in clinical and economic evaluations based on experimental, observational and modelling studies using UK populations. Overall self-rated health status was also collected using the $EQ\text{-}5D_{vas}$ visual analogue score (0 equals worst health and 100 equals best health).

Short Form 36

The SF-36 contains 36 items/questions that measure HRQoL across eight domains: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health (general mood or affect including anxiety, depression and psychological well-being), energy/vitality, bodily pain and general health perceptions. For each dimension, question responses were coded, scored and transformed into a scale from 0 (worst possible score) to 100 (best possible score). The SF-36 items were combined into physical and mental component summary scores using recommended procedures.[45]

The Short Form 6D (SF-6D), a single index preference-based measure, was also derived from the SF-36 responses using the Brazier algorithm.[59] This provided a further summary measure of the SF-36 items using a health-state valuation model that complements the EQ-5D. As it is based on the broader and more detailed SF-36 items, and has a strong theoretical and methodological basis, the SF-6D enabled us to consider whether the level of and change in patients' perception of their well-being following randomisation was similar across these two leading preference-based measures of well-being.

Vascular Quality of Life Questionnaire

The VascuQoL is a disease-specific questionnaire designed to assess specific elements of HRQoL for individuals with lower limb ischaemia. It includes 25 items (questions) subdivided into five domains: pain (four questions), symptoms (four questions), activities (eight questions), social (two questions) and emotional (seven questions). Each question has a seven-point response scale ranging from 1 (worst possible) to 7 (best possible). Responses were averaged for individual domain and composite total scores giving equal weight to each question and domain.

Missing values

We report analyses using available data for all HRQoL end points (case-wise deletion of observations when HRQoL scores were missing). We expected that attrition over time would occur as the horizon for follow-up increased and that missing scores would become more prevalent as trial participants dropped out or failed to complete/return questionnaires. Disregarding observations with missing scores wastes data, reduces power and possibly produces biased estimates of key parameters like the EQ-5D. We therefore employed an imputation method for missing values using all available information following multivariate imputation by chained equations[60,61] for missing $EQ\text{-}5D_{index}$ scores that were used in the QALY analysis. We chose this multiple imputation approach because it has attractive theoretical and methodological properties and is a more powerful and flexible tool when the level of missingness is around 10–60%.

The multivariate imputation model assumes that missing data are missing at random, i.e. that a value being missing may depend on the observed data but not the unobserved data and that the observed data can be used to generate information about the missing values. The multivariate imputations were generated by applying sequential linear regressions, where each incomplete variable was imputed conditionally on all variables in an iterative way. The procedure for selecting variables for predicting missing values was based on using variables with the highest bivarate correlations with the variable being predicted. Redundant variables that added little to the predictions were dropped as were highly collinear variables. We estimated missing values for each of the six EQ-5D scores (baseline, 3, 6 12, 24 and 36 months) using the other five EQ-5D scores, the natural log of survival times and gender. Age and survival status at 3 years were considered but were eliminated from the final prediction equations. We did not include any other variables that could predict missingness in the model. We chose a relatively high number of imputations (10) to increase the efficiency of estimates given the high rate of missingness in the EQ-5D scores. The results were then pooled across the imputed complete data sets using average values for EQ-5D scores.

The QALYs were calculated on an individual patient basis using the $EQ\text{-}5D_{index}$. Specifically, a standard multiplicative model was used to estimate QALYs by the area under linear interpolation of the $EQ\text{-}5D_{index}$ trajectory for each individual using the intervals in months [0, 3], [3, 6], [6, 12], [12, 24] and [24, 36]. These utility-adjusted survival time intervals were summed to generate a total QALY score for each patient. Although, as described in Chapter 3, we did measure survival beyond 3 years (all patients were followed for a minimum of 3 years and 54% for 5 years) and did collect some HRQoL data for a longer time, we chose not to estimate QALYs beyond 3 years from randomisation because of the incomplete clinical follow-up coupled with an increase in the proportion of HRQoL non-responders.

Inpatient hospital use and cost

Resource-use data were collected following randomisation on the index intervention and all subsequent interventions, hospital stays and hospital clinic visits (see data capture forms in Appendix 3). Patient-specific hospital use was measured using the overall duration of stay for each hospital inpatient episode and the number of day-patient/outpatient visits. Acute hospital inpatient days were disaggregated by surgical and medical specialty (e.g. vascular surgery, HDU, ITU, cardiology, general medicine, rehabilitation) based on the reasons for admission and recorded interventions/procedures. Hospital activity data were recorded in all of the participating centres on an individual patient basis. Cumulative hospital episodes, days and visits were restricted to 1, 3 and 7 years from the date of randomisation. These measures of hospital resource use were converted into cost estimates using NHS hospital costs derived routinely for Scotland – a region of the UK that accounted for 31% (142/452) of randomised patients in the trial. The inpatient days, broken down by specialty, were valued using the average specialty-specific cost per day obtained from the Scottish system of hospital cost statistics.[54] Day-

patient/outpatient visits were costed on a per diem/attendance basis.

All procedure costs (surgical, radiological and amputations) were measured using patient-specific anaesthetic, theatre and recovery suite timings, the number and grades of medical, nursing and theatre staff and the specific procedure-related equipment and consumables.

Data capture forms in Appendix 3 show the details of what was recorded. Staff time was valued using UK national pay scales. Purchase costs were used to value the typical mix of equipment and consumables used in the surgical and radiological procedures.

Hospital-use and procedure costs were calculated on a price base of the financial year 2006–7 in UK pounds sterling. A discount rate of 3.5% recommended by HM Treasury was used to calculate the present value of annual costs incurred over 3-year and 7-year time horizons from the date of randomisation. We discounted health effects at 3.5% following current guidance from the National Institute for Health and Clinical Excellence (NICE) suggesting that both costs and health effects should be discounted using a uniform rate. We also estimated undiscounted health effects as arguments continue about the theoretical rationale and methodological implications of differential discounting of costs and effects in economic evaluations of health programmes.

Analysis of HRQoL and hospital costs

Descriptive statistics were based on baseline and follow-up HRQoL questionnaires for cases with no missing items (fewer than 1% of completed questionnaires had missing items). Unadjusted differences in mean EQ-5D weighted scores, SF-36 component summary scores and VascuQoL total scores were assessed using simple linear regressions. Adjusted differences allowing for baseline scores were based on a nearest-neighbour matching estimator.[46] As simple matching estimators are biased when the matching is not exact, a bias-corrected matching estimator was used which adjusts the difference within the matches for the differences in their covariate values.

Arithmetic mean and median costs based on all patients were calculated using the full sample method with no allowance for right censored cases. Given the complete follow-up to at least 3 years for all cases, censoring would have no effect on costs truncated at this point. The impact of right censored cases for longer follow-up is unclear as standard life-table methods may generate bias in estimates of mean costs (and mean survival and quality-adjusted survival times) when informative censoring is present (i.e. patients may incur higher costs in close proximity to death).

Confidence intervals for estimated untransformed arithmetic mean costs were estimated analytically and empirically using bootstrapping techniques to check for the adequacy of the assumptions made regarding the normality of the cost distributions. We found that standard t tests and t test-based confidence intervals were very similar to those based on the bootstrap. We did not allow for any arbitrary differences in the cost per inpatient day or the cost of treatment for specific interventions (e.g. radiological or surgical procedures) using deterministic sensitivity analyses as we felt that the stochastic uncertainty around our cost estimates would easily encompass such assumptions. For example, increasing/decreasing the cost of hospital treatment by an arbitrary 10% for interventions where we might expect service use to be more/less resource-intensive across the 26 centres would in any case have little material impact on the confidence intervals surrounding the point estimate of the difference in average total costs. Extreme value analysis of single (or multiple) resource parameters was not conducted nor did we try to calculate threshold values leading to a convergence or even reversal of the cost estimates that we present for each trial arm.

Cost-effectiveness measures

Incremental cost-effectiveness ratios were estimated using the mean difference in hospital costs and the mean difference in effectiveness between the angioplasty and surgery groups. We considered a range of effectiveness measures using mean differences in AFS (the primary end point of the trial) in days, mean differences in OS and patient-specific total QALYs to 36 months based on the EQ-5D. To capture the uncertainty surrounding the estimate of mean differences in costs and effects we used both analytical and non-parametric bootstrap methods. We report the joint distribution of differences in costs and effects using analytical methods based on a bivariate normal distribution allowing for covariance between mean cost and effect differences. Visual presentations of cost-effectiveness are reported using confidence ellipses (50%, 90% and 95%) to capture the magnitude

and precision of differences in costs and effects. Scatterplots of incremental costs and effects and corresponding confidence ellipses based on a non-parametric bootstrap technique were also calculated using 5000 resamples of the difference in cost and effects drawn with replacement from the original sample of patients. We also summarise our cost-effectiveness results within a net benefit approach using incremental net (monetary) benefit and cost-effectiveness acceptability curves. Net benefit in this framework is defined as the monetary equivalent of the incremental health effects less incremental costs. The monetary equivalent of the health effects is the product of decision-makers' willingness to pay (WTP) for a one unit gain in health benefit (e.g. £30,000 per QALY) and the health benefit (e.g. amputation-free life-year, life-year or QALY gained). As the WTP value per unit of health benefit is generally unknown or will vary between decision-makers, the estimated net monetary benefit is calculated and plotted for different values of WTP. The standard interpretation is that a treatment is cost-effective if the net monetary benefit is greater than zero. When the joint distribution is (roughly) centred on zero, there may be no monetary values attached to the health outcome where a reasonable percentage of the joint distribution is cost-effective/cost-ineffective. We addressed this possibility by estimating cost-effectiveness acceptability curves that present the probability that the alternative is cost-effective (the net monetary benefit is positive) allowing for different ceiling values for a decision-maker's WTP per unit of health benefit.

All health economic analyses were conducted using STATA Statistical Software, release 10. Imputations for missing EQ-$5D_{index}$ scores were generated using an algorithm for creating models for imputation (STATA packages pred_eq and check_eq and the STATA ice package).[62]

HRQoL results

SF-36 health dimensions and summary scores

The SF-36 domains and summary scores [based on 213/224 (95%) responders in the angioplasty group and 207/228 (91%) responders in the surgery group with complete questionnaires] were similar in the two trial arms at baseline (before randomisation) although those subsequently randomised to bypass surgery appeared to have very marginally, probably clinically insignificantly, better HRQoL (Table 41).

The distributions were generally positively skewed with evidence of moderate positive kurtosis, reflecting relatively peaked distributions. At baseline, BASIL patients perceived their health to be much lower than that reported in general populations (matched for age and gender) and patients undergoing endovascular or conventional aortic aneurysm repair.[63] Large floor effects (proportion of patients in the worst possible health states) were observed for the role physical (82%) and role emotional (61%) scales. With the exception of role emotional (29%), ceiling effects (proportion of patients in the best possible heath state) were small and well below 10% for most scales.

Patients in both treatment groups reported improved SF-36 scales and summary scores by 3 months (Table 42), but little improvement was recorded beyond 3 months. Most of the gains in SF-36 are concentrated in the scales which capture perceptions of physical well-being. However, there is also a very large increase in the emotional dimension of the SF-36 and there is some slight improvement over a longer time period in the SF-36 mental health domain.

Vascular Quality of Life Questionnaire

The disease-specific VascuQoL scales provide further evidence that both angioplasty and surgery have a positive impact on all domains affected by SLI (Table 43).[64] As with the SF-36, the VascuQoL domains all record higher scores (better HRQoL) at baseline in those that are subsequently randomised to surgery. This is maintained and, in fact, disease-specific HRQoL is better in those randomised to surgery in every domain and at every time point out to 24 months. Interestingly, at 36 months, this reverses and angioplasty appears to be associated with superior HRQoL (Figure 22).

The question is whether surgery affords some advantage over angioplasty in terms of generic and, perhaps more relevantly, disease-specific HRQoL at least in the short term (12–24 months). Unadjusted mean VascuQoL total scores by trial arm at baseline (before randomisation) and various time points thereafter are shown in Figure 22. Overall, these data suggest that any advantage to surgery may be largely due to the surgery group having a slightly better HRQoL at baseline rather due to any additional benefit from bypass surgery over balloon angioplasty in terms of HRQoL.

TABLE 41 *Descriptive statistics for SF-36 domains and summary scores at baseline (before randomisation)*

SF-36 domains		*n*	Mean	Median	Range	SD	Skewness	Kurtosis	Floor (%)	Ceiling (%)
Physical functioning	Angioplasty	213	22.68	20.00	0–95	19.35	1.16	4.00	9.86	0.47
	Surgery	207	22.97	20.00	0–90	19.80	1.03	3.92	15.46	0.97
Social functioning	Angioplasty	213	40.43	37.50	0–100	28.42	0.46	2.41	12.68	6.57
	Surgery	207	44.75	50.00	0–100	31.53	0.23	1.98	14.49	9.66
Role physical	Angioplasty	213	10.21	0.00	0–100	25.44	2.58	8.64	82.16	4.69
	Surgery	207	13.41	0.00	0–100	29.43	2.21	6.54	77.29	8.21
Role emotional	Angioplasty	213	31.30	0.00	0–100	42.72	0.80	1.83	61.03	23.94
	Surgery	207	36.71	0.00	0–100	44.48	0.55	1.47	55.07	28.99
Mental health	Angioplasty	213	58.65	60.00	0–100	22.90	−0.33	2.41	0.47	1.88
	Surgery	207	60.31	60.00	0–100	21.40	−0.37	2.43	0.48	0.97
Energy/vitality	Angioplasty	213	34.11	35.00	0–90	20.74	0.28	2.52	7.04	1.41
	Surgery	207	36.76	40.00	0–85	21.00	0.15	2.15	3.38	0.97
Bodily pain	Angioplasty	213	28.61	22.00	0–100	20.28	0.89	4.12	11.74	1.41
	Surgery	207	30.25	31.00	0–100	21.15	0.49	2.92	15.46	0.48
General health	Angioplasty	213	48.98	47.00	5–100	19.90	0.12	2.49	0.47	0.47
	Surgery	207	48.42	50.00	0–100	21.58	−0.05	2.14	0.48	0.48
PCS	Angioplasty	213	17.50	16.03	3.13–47.86	7.97	1.09	4.37	0.00	0.00
	Surgery	207	17.80	17.33	–0.15–46.92	9.06	0.64	3.60	0.00	0.00
MCS	Angioplasty	213	43.47	43.37	16.98–74.68	11.64	−0.01	2.35	0.00	0.00
	Surgery	207	45.17	44.37	18.22–72.09	11.96	0.11	2.18	0.00	0.00

MCS, mental component summary; PCS, physical component summary.
Based on 213/224 (96%) patients in the angioplasty group and 207/228 (91%) patients in the surgery group with complete questionnaires. Includes four lost to follow-up.

TABLE 42 *Unadjusted SF-36 domain scores by intention-to-treat analysis at different time points from randomisation*

		Baseline		3 months	
		Angioplasty	**Surgery**	**Angioplasty**	**Surgery**
Returned questionnaires[a]		(*n* = 212)	(*n* = 203)	(*n* = 162)	(*n* = 152)
Number alive		223	225	204	199
Response rate		95%	90%	79%	76%
Physical functioning	mean	22.69	23.04	30.77	32.43
	SD	19.39	19.91	25.44	26.55
Social functioning	mean	40.63	44.24	55.32	57.81
	SD	28.36	31.37	31.58	30.92
Role physical	mean	10.26	13.11	25.46	23.03
	SD	25.49	28.99	38.56	36.00
Role emotional	mean	31.45	36.27	51.65	49.78
	SD	42.77	44.29	45.21	45.07
Mental health	mean	58.87	60.08	65.93	68.55
	SD	22.73	21.42	19.84	20.38
Energy/vitality	mean	34.15	36.32	42.28	44.61
	SD	20.78	20.81	24.21	23.48
Bodily pain	mean	30.40	31.97	55.21	57.31
	SD	21.68	22.90	27.92	27.96
General health	mean	49.14	48.04	50.06	52.37
	SD	19.81	21.51	20.67	22.22

a Scores are based on completed questionnaires with no missing items (four cases lost to follow-up not included).

TABLE 43 *Unadjusted VascuQoL domain and overall scores by intention-to-treat analysis at different time points from randomisation*

		Baseline		3 months	
		Angioplasty	**Surgery**	**Angioplasty**	**Surgery**
Returned questionnaires[a]		(*n* = 214	(*n* = 204	(*n* = 161	(*n* = 153
Number alive		223	225	204	199
Response rate		96%	91%	79%	77%
Health domain					
Activity	mean	2.33	2.45	3.65	3.87
	SD	0.98	1.07	1.56	1.49
Symptoms	mean	3.63	3.73	5.11	5.33
	SD	1.42	1.40	1.22	1.16
Pain	mean	2.34	2.48	4.50	4.72
	SD	1.21	1.30	1.73	1.68
Social	mean	2.83	3.08	4.16	4.45
	SD	1.58	1.82	2.03	1.83
Emotional	mean	3.06	3.13	4.58	4.80
	SD	1.33	1.45	1.60	1.54
Overall	mean	2.79	2.90	4.32	4.55
	SD	1.01	1.10	1.39	1.30

a Scores are based on completed questionnaires with no missing items (four cases lost to follow-up not included.

6 months		12 months		24 months		36 months	
Angioplasty	**Surgery**	**Angioplasty**	**Surgery**	**Angioplasty**	**Surgery**	**Angioplasty**	**Surgery**
(*n* = 143)	(*n* = 131)	(*n* = 132)	(*n* = 119)	(*n* = 63)	(*n* = 76)	(*n* = 48)	(*n* = 49)
192	185	179	170	159	147	134	138
75%	71%	74%	70%	40%	52%	36%	36%
33.85	33.74	33.60	37.39	35.87	38.09	35.10	31.94
25.17	26.58	24.51	29.21	29.90	32.04	27.76	30.05
53.41	57.06	59.85	61.97	58.53	59.87	61.98	56.12
32.61	32.67	26.63	29.85	34.40	31.18	27.53	36.10
30.59	26.15	30.11	31.51	31.75	29.93	26.56	25.51
39.18	37.58	39.41	38.85	38.42	41.44	42.65	39.36
50.58	55.22	52.02	58.82	52.38	53.95	55.56	46.94
45.25	44.29	45.17	42.23	43.47	45.86	47.31	46.61
65.43	67.02	68.67	70.52	72.76	69.32	70.33	67.18
21.87	19.86	21.41	18.85	19.25	18.46	20.71	20.22
41.61	44.62	41.21	47.56	43.57	43.95	44.79	44.59
23.81	22.21	23.88	21.62	23.73	20.82	24.28	25.14
53.85	57.76	54.29	60.04	54.32	58.48	56.94	55.10
28.04	28.26	25.78	27.53	30.21	29.16	25.07	31.51
48.00	51.73	48.96	50.76	49.25	48.55	48.21	46.51
22.48	23.14	21.79	20.01	21.12	23.22	18.46	21.34

6 months		12 months		24 months		36 months	
Angioplasty	**Surgery**	**Angioplasty**	**Surgery**	**Angioplasty**	**Surgery**	**Angioplasty**	**Surgery**
(*n* = 142	(*n* = 131	(*n* = 132	(*n* = 121	(*n* = 62	(*n* = 78	(*n* = 46	(*n* = 49
192	185	179	170	159	147	134	138
74%	71%	74%	71%	39%	53%	34%	36%
3.64	3.83	3.79	3.93	3.78	3.95	3.85	3.71
1.46	1.57	1.57	1.55	1.69	1.75	1.65	1.72
5.04	5.31	5.28	5.35	5.31	5.39	5.43	5.16
1.19	1.09	1.18	1.27	1.36	1.28	1.13	1.23
4.42	4.71	4.65	4.84	4.95	4.97	4.78	4.58
1.73	1.68	1.72	1.73	1.71	1.62	1.50	1.73
4.06	4.24	4.43	4.64	4.30	4.49	4.33	4.20
1.97	1.94	1.95	1.77	2.04	2.06	1.85	2.08
4.61	4.89	4.90	5.06	4.95	5.15	5.00	4.86
1.64	1.47	1.68	1.54	1.65	1.61	1.63	1.79
4.30	4.54	4.53	4.67	4.58	4.72	4.61	4.44
1.38	1.34	1.42	1.37	1.53	1.50	1.41	1.55

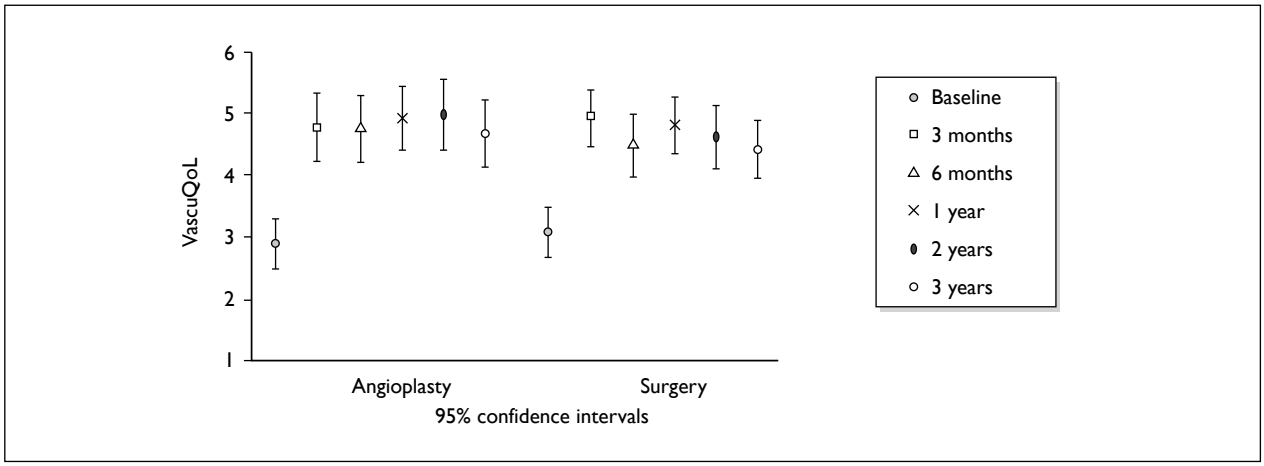


FIGURE 22 *Unadjusted mean VascuQoL total scores by trial arm at baseline (before randomisation) and various time points thereafter.*

EuroQoL and SF-6D

This general pattern of improvement is also reflected in the EuroQoL and SF-6D weighted index scores (Table 44).

Summary

Although there is some weak evidence that HRQoL may be somewhat better in the bypass surgery group, there are no significant differences in HRQoL when the two treatment groups are compared; especially when post-randomisation scores are adjusted for differences in scores at baseline (before randomisation). Furthermore, the HRQoL from surviving responders is likely to be substantially better than that for the trial cohort as a whole and in each trial arm separately.

Crude and adjusted differences in SF-36 (Table 45), VascuQoL (Table 46), EQ-5D and SF-6D (Table 47) scores are very similar and not significantly different from zero at all time intervals up to 36 months. Patients in both treatment groups reported virtually identical levels and trajectories in the EQ-5D and SF-6D over time.

Imputation of missing values

As might have been expected, HRQoL response rates fell significantly over time. Data for the EQ-5D, used to undertake the cost per QALY analysis, are shown in Table 48; response data for the other HRQoL instruments were very similar. In other words, individual patient response rates were similar across all the questionnaires that they were

TABLE 44 *EuroQoL and SF-6D scores by intention-to-treat analysis at different time points from randomisation*

		Baseline		3 months	
		Angioplasty	**Surgery**	**Angioplasty**	**Surgery**
Returned questionnaires[a]		(*n* = 214)	(*n* = 203)	(*n* = 162)	(*n* = 152)
Number alive		223	225	204	199
Response rate		96%	91%	79%	77%
EuroQoL					
EQ-5D	mean	0.26	0.28	0.53	0.57
	SD	0.32	0.34	0.31	0.28
EQ-VAS	mean	0.53	0.55	0.60	0.62
	SD	0.21	0.21	0.20	0.19
SF-6D	mean	0.53	0.54	0.60	0.61
	SD	0.10	0.11	0.13	0.13

EQ-5D, weighted index score; EQ-VAS, visual analogue scale; SF-6D, weighted index score.
a Scores are based on completed questionnaires with no missing items (four cases lost to follow-up not included).

asked to complete. Response rates in the two arms were very similar.

Although all patients known to still be alive were asked to complete the HRQoL questionnaires, perhaps not surprisingly, those patients who had already undergone major limb amputation were less likely to respond. It may also be reasonable to presume that those with the lowest HRQoL, many of whom were under continuing hospital care for their SLI and a range of other comorbidities, were less likely to return their questionnaires. So it may be that the data restricted to complete cases only present an overoptimistic picture of the results of the intervention; in other words, those patients who are doing well (after both balloon angioplasty and bypass surgery) may be substantially over-represented among the responders.

Without the multiple imputations and using only complete data, we would have only been able to analyse a very small number of cases. We considered it more sensible to use all of the available information, conduct the multiple imputations using appropriate methods and then analyse the distribution of EQ-5D scores using complete data based on actual and imputed values.

Table 49 provides imputed and recorded mean EQ-5D scores at time intervals up to 3 years following randomisation. The complete data imputed for patients who were alive and could have returned questionnaires is also presented for individuals by amputation status. There is very little difference between the mean scores calculated for recorded data and imputed data at baseline and early periods following randomisation (< 12 months) where the degree of 'missingness' is relatively low. As the response rates deteriorated over time, the scores based on complete imputed data are lower than those based solely on the complete recorded data. A widening gap also emerged between the imputed scores for survivors with or without an amputation. The individuals without an amputation appeared to fare better with higher EQ-5D scores compared with survivors with an amputation who could have completed this measure of self-reported well-being. Table 50 compares the treatment groups using the imputed EQ-5D scores. There is a small but persistent advantage in favour of surgery when the EQ-5D is assessed at all time intervals up to 3 years. These data are summarised graphically in Figure 23.

Results: resource utilisation

Hospital admissions and length of stay

The use of inpatient hospital services over time was broadly similar for patients in both trial arms as measured by the number of hospital admissions and total days spent in hospital (Table 51). Over the first year from randomisation, patients in the surgery group were in hospital for about a week longer than those in the angioplasty group. The difference in hospital stay shifted in favour of surgery over the longer run as the angioplasty patients used slightly more inpatient care over the medium to long run. Over a 7-year time

6 months		12 months		24 months		36 months	
Angioplasty	**Surgery**	**Angioplasty**	**Surgery**	**Angioplasty**	**Surgery**	**Angioplasty**	**Surgery**
(*n* = 143)	(*n* = 131)	(*n* = 132)	(*n* = 119)	(*n* = 63)	(*n* = 76)	(*n* = 48)	(*n* = 49)
192	185	179	170	159	147	134	138
74%	71%	74%	71%	39%	53%	34%	36%
0.52	0.57	0.56	0.62	0.56	0.59	0.61	0.54
0.33	0.31	0.31	0.28	0.33	0.34	0.25	0.35
0.59	0.65	0.60	0.64	0.61	0.63	0.63	0.61
0.20	0.20	0.20	0.19	0.20	0.22	0.21	0.19
0.61	0.61	0.63	0.63	0.62	0.64	0.64	0.60
0.14	0.13	0.13	0.12	0.15	0.14	0.14	0.15

TABLE 45 *Comparison of SF-36 physical and mental component summaries by intention-to-treat analysis*

	Angioplasty (*n* = 224)	Surgery (*n* = 228)	Crude difference, mean (SE)	Difference adjusted for baseline score, mean (SE, number of patients)	*p*-value
SF-36 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)	
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
12–24 months	31.57 (11.72, 63)	32.61 (11.87, 76)	1.04 (2.01)	2.42 (1.96, 133)	0.22
24–36 months	31.19 (10.08, 48)	30.98 (11.89, 49)	0.21 (2.24)	–0.92 (2.17, 94)	0.67
SF-36 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
12–24 months	48.51 (10.89, 63)	47.67 (10.43, 76)	0.85 (1.81)	–1.89 (1.62, 133)	0.24
24–36 months	49.01 (11.84, 48)	46.73 (12.04, 49)	2.27 (2.43)	–4.42 (2.47, 94)	0.07

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

TABLE 46 *Comparison of VascuQoL overall score by intention-to-treat analysis*

	Angioplasty (*n* = 224)	Surgery (*n* = 228)	Crude difference, mean (SE)	Difference adjusted for baseline score, mean (SE, number of patients)	*p*-value
VascuQoL					
Baseline	2.78 (1.01, 215)	2.91 (1.10, 207)	0.13 (0.10)	1	
0–3 months	4.32 (1.39, 162)	4.55 (1.30, 153)	0.23 (0.15)	0.17 (0.14, 306)	0.22
3–6 months	4.28 (1.38, 143)	4.54 (1.34, 131)	0.26 (0.16)	0.19 (0.15, 268)	0.20
6–12 months	4.53 (1.42, 133)	4.67 (1.37, 121)	0.14 (0.18)	0.02 (0.17, 248)	0.91
12–24 months	4.58 (1.53, 62)	4.72 (1.50, 78)	0.14 (0.25)	0.14 (0.28, 134)	0.63
24–36 months	4.61 (1.41, 46)	4.44 (1.55, 49)	0.17 (0.30)	–0.39 (0.30, 92)	0.20

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

horizon the average number of hospital stays for both groups was four and average length of stay, averaged over all inpatient admissions, was just over 2 months (71 days). It is striking, therefore, that on average, these patients spent the best part of 5–6 weeks of their first post-randomisation year in hospital; then 2–3 weeks per year thereafter. It is worth noting that these data reflect only acute hospital resource use and exclude time spent, for example, in 'step-down' facilities for rehabilitation after amputation.

Given the additional short-term morbidity of surgery (see Chapter 2), there is less of a difference between the two trial arms than might perhaps have been expected. However, these data probably reflect the fact that there is a range of (medical and social) factors, other than the status of the trial leg and its treatment, that determine admission, readmission and length of stay in hospital, and patients randomised to angioplasty have a significantly higher immediate failure and reintervention rate (see Chapter 2).

TABLE 47 *Comparison of EQ-5D and SF-6D index scores by intention-to-treat analysis*

	Angioplasty (*n* = 224)	Surgery (*n* = 228)	Crude difference, mean (SE)	Difference adjusted for baseline score, mean (SE, number of patients)	*p*-value
EQ-5D 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
12–24 months	0.56 (0.32, 63)	0.59 (0.34, 76)	0.03 (0.06)	0.08 (0.06, 132)	0.16
24–36 months	0.61 (0.25, 48)	0.54 (0.35, 49)	0.07 (0.06)	–0.06 (0.05, 93)	0.29
SF-6D weighted index score					
Baseline	0.53 (0.10, 213)	0.54 (0.11, 207)	0.01 (0.01)	1	
0–3 months	0.60 (0.13, 163)	0.61 (0.13, 152)	0.00 (0.01)	0.01 (0.01, 304)	0.68
3–6 months	0.61 (0.13, 144)	0.61 (0.13, 131)	0.00 (0.02)	0.00 (0.02, 267)	0.92
6–12 months	0.62 (0.13, 133)	0.63 (0.12, 119)	0.01 (0.02)	0.00 (0.02, 245)	0.86
12–24 months	0.62 (0.15, 63)	0.64 (0.14, 76)	–0.01 (0.02)	0.01 (0.03, 133)	0.61
24–36 months	0.64 (0.14, 48)	0.60 (0.15, 49)	0.04 (0.03)	–0.05 (0.03, 94)	0.08

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

TABLE 48 *EQ-5D drop out rates*

	EQ-5D Mean score (actual data)	EQ-5D completed	No EQ-5D available	Major amputation of trial limb	Dead	Dropped out	Total cohort size
Angioplasty							
Baseline	0.2604	215	8	0	1	9	224
3 months	0.5295	163	28	16	17	61	224
6 months	0.5182	144	34	20	26	80	224
12 months	0.5544	133	27	24	40	91	224
24 months	0.5576	63	79	21	61	161	224
36 months	0.6113	48	75	17	84	176	224
Surgery							
Baseline	0.2884	206	22	0	0	22	228
3 months	0.5709	152	41	11	24	76	228
6 months	0.5682	131	47	19	31	97	228
12 months	0.6167	119	36	22	51	109	228
24 months	0.5885	76	65	17	70	152	228
36 months	0.5405	49	79	17	83	179	228

TABLE 49 *Imputed and recorded EQ-5D mean scores (n) from baseline to 36 months' follow-up showing effect of amputation*

		Imputed scores[a]		Recorded scores[a]
Follow-up month/days[b]	Dead	Alive with amputation[c]	Alive with no amputation	Alive with no amputation
Baseline	na	na	0.274 (452)	0.274 (421)
3 months/116 days	na (45)	0.514 (30)	0.549 (377)	0.550 (315)
6 months/212 days	na (71)	0.500 (39)	0.543 (342)	0.543 (273)
12 months/398 days	na (99)	0.532 (43)	0.584 (310)	0.585 (251)
24 months/774 days	na (143)	0.478 (39)	0.544 (271)	0.581 (137)
36 months/1118 days	na (176)	0.435 (38)	0.528 (238)	0.594 (90)

na, not applicable.
a Imputed scores were derived from the whole population (amputees and intact patients) for whom recorded data were available (i.e. all those patients who returned completed questionnaires); there is no column for recorded scores (alive with amputation) because very few patients alive with amputation provided HRQoL data following their amputation because of poor postamputation survival and low response rates in those that did survive.
b Average number of days following randomisation when EQ-5D scores were recorded.
c Amputation of trial leg.

TABLE 50 *Imputed EQ-5D mean scores (n) by treatment group from baseline to 36 months' follow-up showing effect of randomised treatment*

	Angioplasty		Surgery	
Follow-up month/days[a]	Dead	Alive	Dead	Alive
Baseline	na	0.262 (224)	na	0.287 (228)
3 months/116 days	na (19)	0.533 (205)	na (26)	0.561 (202)
6 months/212 days	na (31)	0.527 (193)	na (40)	0.550 (188)
12 months/398 days	na (44)	0.558 (180)	na (55)	0.598 (173)
24 months/774 days	na (64)	0.518 (160)	na (78)	0.555 (150)
36 months/1118 days	na (89)	0.505 (135)	na (87)	0.524 (141)

na, not applicable.
a Average number of days following randomisation when EQ-5D scores were recorded.
Imputed scores were derived from the whole population (amputees and intact patients) for whom recorded data were available (i.e. all those patients who returned completed questionnaires).

TABLE 51 *Mean (SD) and median (interquartile range) hospital admissions and length of stay*

	Angioplasty (*n* = 223)		Surgery (*n* = 225)	
	Mean	Median	Mean	Median
Hospital admissions				
Year 1	2.1 (1.5)	2 (1 to 3)	2.2 (1.4)	2 (0 to 2)
Years 2–3	1.1 (1.8)	0 (0 to 2)	1.0 (1.5)	0 (0 to 1)
Years 4–7	0.8 (1.7)	0 (0 to 1)	0.9 (1.9)	0 (0 to 1)
Years 1–7	4.1 (3.5)	3 (2 to 5)	4.1 (3.3)	3 (2 to 5)
Hospital stays (days)				
Year 1	36.5 (55.5)	16 (4 to 46)	45.1 (54.1)	27 (12 to 60)
Years 2–3	20.4 (48.6)	0 (0 to 20)	14.8 (29.4)	0 (0 to 15)
Years 4–7	14.7 (43.4)	0 (0 to 5)	11.3 (26.4)	0 (0 to 4)
Years 1–7	71.5 (102.4)	37 (13 to 87)	71.2 (73.2)	48 (21 to 91)

Excludes data on four patients lost to follow-up.

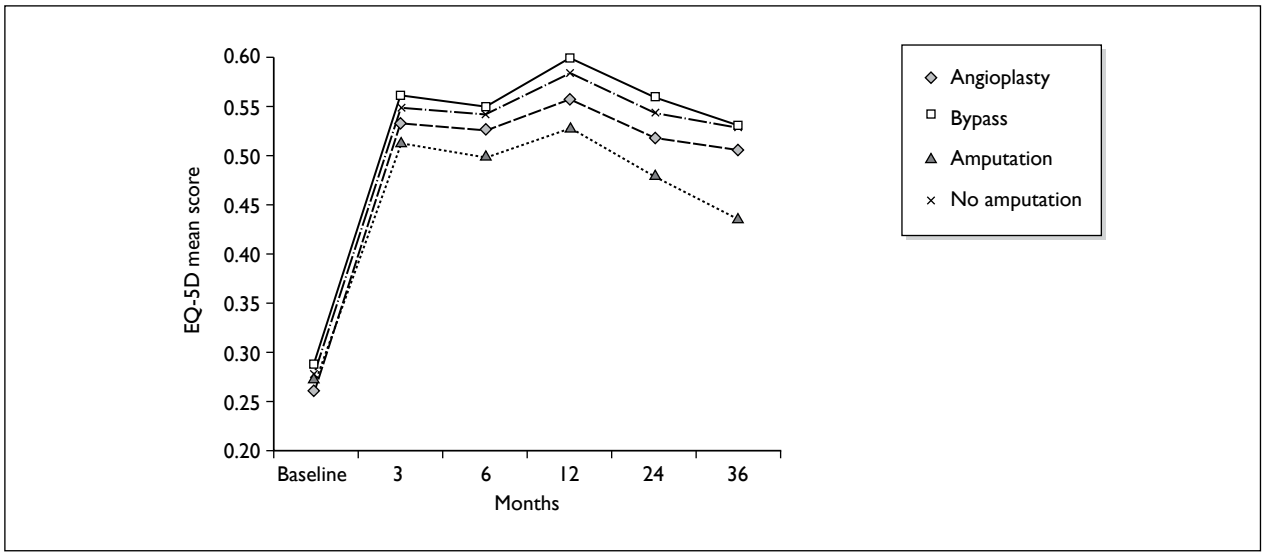


FIGURE 23 *Imputed EQ-5D mean scores (n) by treatment group from baseline to 36 months follow-up showing effect of amputation and of randomised treatment.*

Patients' inpatient episodes primarily occurred in ward settings with very little use of the more specialised services provided in HDU and ITU (Table 52). Patients randomised to a surgery-first strategy used around a half day more of HDU on average compared with angioplasty-first patients. There is a slight difference in ITU use with a few additional hours used by the surgery-first patients.

TABLE 52 *Mean (SD) length of stay (days) in wards, high dependency units (HDUs) and intensive therapy units (ITUs) by treatment group*

	Angioplasty (*n* = 223)	Surgery (*n* = 225)
Year 1		
Ward	36.3 (55.5)	44.6 (54.0)
HDU	0.2 (1.2)	0.7 (1.6)
ITU	0.0 (0.6)	0.1 (0.9)
Years 2–3		
Ward	20.3 (48.5)	14.7 (29.4)
HDU	0 (0)	0 (0.1)
ITU	0.1 (1.2)	0 (0.2)
Years 1–3		
Ward	56.6 (89.4)	59.4 (64.1)
HDU	0.2 (1.2)	0.7 (1.6)
ITU	0.1 (1.3)	0.2 (1.0)

Excludes data on four patients lost to follow-up.

The main cost driver remains the number and duration of episodes in acute ward settings.

Table 53 presents more detail on the structure of costs incurred in the hospital wards and theatres. After 3 years of follow-up, theatre costs account for 9% of total hospital costs in the angioplasty-first group. As expected, the corresponding figure is higher at 14% for the surgery-first group. Most of the theatre and hospital ward costs fall in the first year following randomisation.

Hospital costs

Over the first year from randomisation the mean cost of inpatient hospital treatment in patients randomised to surgery was estimated as £22,002 (£18,369 hospital stay and £3635 procedure costs), which is approximately a third higher than the £16,582 (£14,468 hospital stay and £2115 procedure costs) for patients randomised to angioplasty (see Chapter 2) (Table 54). This difference in mean total hospital and procedure costs of around £5420 was significant (95% CI £1547 to £9294) at 1 year. However, because of increased costs incurred by the angioplasty patients in subsequent years, at the end of 7 years this difference decreased to £2310 (£33,539 surgery vs £31,228 angioplasty) and was no longer significant (see Chapter 3). The median cost of inpatient hospital treatment showed a slightly different pattern, with significant differences emerging in favour of angioplasty (i.e. lower median costs) for the first year following randomisation and for cumulative costs up to 7 years (£24,959 surgery versus £18,256 angioplasty).

TABLE 53 *Mean (SD) ward, procedure and total hospital costs by randomised group*

Hospital costs per patient	Angioplasty (*n* = 223)	Surgery (*n* = 225)
Year 1		
Ward costs (including HDU, ITU)	£14,467 (£20,552)	£18,369 (£19,536)
Procedure costs	£2115 (£2148)	£3634 (£2281)
Total hospital costs	£16,582 (£21,419)	£22,002 (£20,286)
Years 2–3		
Ward costs (including HDU, ITU)	£8596 (£18,274)	£6484 (£13,333)
Procedure costs	£294 (£831)	£520 (£1400)
Total hospital costs	£8890 (£18,500)	£7003 (£13,753)
Years 1–3		
Ward costs (including HDU, ITU)	£23,064 (£31,603)	£24,853 (£24,829)
Procedure costs	£2409 (£2328)	£4153 (£2806)
Total hospital costs	£25,472 (£32, 453)	£29,006 (£25,572)

UK £s using 2006–7 values, undiscounted; excludes data on four patients lost to follow-up.

Results: amputation-free survival, overall survival and quality-adjusted survival

As reported in Chapters 2 and 3, taking the follow-up period as a whole, there was little difference in AFS or OS between the two groups. The differences in mean AFS or OS days calculated over 7 years are between 3 and 4 weeks (Table 55). Discounting these health effects at 3.5% reduces the differences in survival days by just over 1 week. These differences favour the surgery group but are not significant. However, while the risk of death was non-significantly higher in the surgery group up to 2 years, after 2 years the risk of death was significantly higher in those patients who had initially been randomised to angioplasty.

If we now take a 36-month perspective (the time point up to which we had 100% clinical follow-up save the four patients lost to follow-up) there are small and statistically insignificant differences in restricted mean AFS and OS when calculated over 3 years (Table 55).

When combined with patient-specific EQ-5D scores, these absolute differences in survival lead to virtually no difference in the number of quality-adjusted life (days) between the two trial arms.[65]

The small positive differences in HRQoL in favour of surgery as measured by $EQ\text{-}5D_{index}$ when combined with absolute survival in the two groups out to 36 months from randomisation generates a mean quality-adjusted life time of 442 days for angioplasty and 452 days for surgery. The mean difference of 10 days (95% CI –48 days to 68 days) fails to achieve conventional levels of significance.

However, when interpreting these data it is important to remember the limitations to the HRQoL data discussed above (low response rates after 12 months, differential factors affecting response rates).

One also needs to bear in mind that these figures are based on HRQoL and absolute mortality over 36 months. We know that the balance of risks and benefits for surgery versus angioplasty changes significantly after 2 years (see Chapter 3) and these longer-term benefits will not be captured completely by this analysis out to 36 months.

As a consequence, it is possible that longer-term (out to 7 years) survival gains (Table 55) might translate into larger differences in quality-adjusted survival in favour of surgery. However, this can only be speculation because the number of patients available for study at 7 years is very small and we do not have HRQoL data beyond 36 months.

TABLE 54 *Mean (95% CI) and median (interquartile range) costs and cost differences between trial arms*

	Hospital cost per patient[a]		
	Angioplasty (*n* = 223)	**Surgery (*n* = 225)**	**Cost difference[b]**
Mean			
Year 1	£16,582 (£13,845 to £19,320)	£22,002 (£19,277 to £24,728)	£5420 (£1547 to £9294)
Years 2–3	£8890 (£6753 to £11,028)	£7003 (£4874 to £9132)	–£1887 (–£4912 to £1138)
Years 4–7	£5756 (£3920 to £7591)	£4533 (£2706 to £6361)	–£1223 (–£3820 to £1374)
Years 1–7	£31,228 (£26,750 to £35,707)	£33,539 (£29,080 to £37,997)	£2310 (–£4027 to £8647)
Median			
Year 1	£9068 (£6884, £11,253)	£15,305 (£13,130, £17,480)	£6236 (£3145 to £9327)
Years 2–7[c]	£3026 (£949, £5104)	£1648 (–£421, £3716)	–£1379 (–£4318 to £1561)
Years 1–7	£18,256 (£14,709, £21,802)	£24,959 (£21,429, £28,490)	£6704 (£1686 to £11,721)

a UK £s 2006–7 values, discounted 3.5%.
b Positive cost difference indicates surgery is more costly compared with angioplasty.
c Median cost for years 2–3 and years 4–7 is zero for both angioplasty and surgery groups.
Excludes data on four patients lost to follow-up.

Results: cost-effectiveness

Point estimates of cost-effectiveness

Point estimates of cost-effectiveness can be calculated by comparing average differences in hospital costs and average differences in treatment effects; in this case AFS and OS at different points in time after randomisation.

Seven-year (non-quality-adjusted) analysis

If we first take a 7-year perspective on (non-quality-adjusted) AFS and hospital costs those patients randomised to surgery are estimated to live, on average, 32 days longer with their trial leg intact at an estimated additional average hospital cost of £2310 when compared with those randomised to angioplasty. The additional cost per AFS year is £26,032 [(£2310/(32.4/365.25)]. Similarly, when the estimated additional hospital cost of surgery out to 7 years (£2310) is compared with the additional estimated average gain in OS (20 days) the cost-effectiveness ratio is £41,401 [£2310/(20.4/365.25)].

Three-year (quality-adjusted) analysis

Taking a three-year perspective, using the available baseline to 36 months HRQoL (imputed EQ-5D) data to perform a quality-adjusted life analysis we find that patients randomised to surgery are estimated to enjoy, on average, an additional 10 quality-adjusted life days at an estimated additional average hospital cost of £3533 when compared with those randomised to angioplasty. This point estimate of the cost-effectiveness over 3 years generates a 'cost per QALY' of £134,257 [£3533/(9.6/365.25)].

Relationship between differences in cost and differences in amputation-free survival

The relationship between bootstrapped estimates of the difference in cost (surgery less angioplasty) between the two trial arms and the differences in amputation-free life-years (surgery less angioplasty) out to 7 years is shown in Figure 24. The interpretation of each quadrant is:

- upper right: surgery more costly with additional AFS days
- lower right: surgery less costly with additional AFS days
- upper left: surgery more costly with fewer AFS days
- lower left: surgery less costly with fewer AFS days.

About half of the distribution (50.2%) is located in the upper right quadrant of the graph (more costly and more effective) but it also extends well into the lower left quadrant (more expensive, fewer amputation-free life-years). A further 26.4%

TABLE 55 *Mean amputation-free survival, overall survival and quality-adjusted survival (95% CI)*

	Balloon angioplasty (*n* = 223)	Bypass surgery (*n* = 225)	Difference
Amputation-free survival (days)[a]			
Undiscounted	1082 (976 to 1188)	1123 (1017 to 1228)	41 (–109 to 190)
Discounted at 3.5%	984 (894 to 1076)	1017 (921 to 1114)	32 (–100 to 165)
Overall survival (days)[a]			
Undiscounted	1248 (1147 to 1348)	1276 (1176 to 1377)	29 (–114 to 171)
Discounted at 3.5%	1134 (1050 to 1219)	1155 (1062 to 1247)	20 (–105 to 146)
Quality-adjusted survival (days)[b]			
Undiscounted	442 (401 to 483)	452 (441 to 493)	10 (–48 to 68)
Discounted at 3.5%	414 (377 to 452)	424 (385 to 464)	10 (–45 to 64)

a Means ≤ 7 years.
b Means ≤ 3 years.

is located in the upper left quadrant (more costly and less effective) with 17.8% in the lower right quadrant (less costly and more effective) and 5.6% in the lower left quadrant (less costly and less effective).

Along with this empirical distribution broken down into the quadrants, we also report confidence ellipses (50%, 75% and 95%) surrounding the point estimate of cost-effectiveness to describe the distribution of incremental costs and effects (Figure 25). These data can, therefore, be used to create a cost-effectiveness acceptability curve,[66] which shows the probability that a surgery-first strategy is cost-effective, assuming different ceiling levels for the value placed on an amputation-free life-year (Figure 25). At a WTP value of £26,032 the probability is equal to 0.5 by construction as this is the point estimate of the cost-effectiveness ratio. The curve is relatively flat beyond this point suggesting that with higher values placed on an additional amputation-free life-year (e.g. > £50,000) the probability that surgery is cost-effective is less than 0.6.

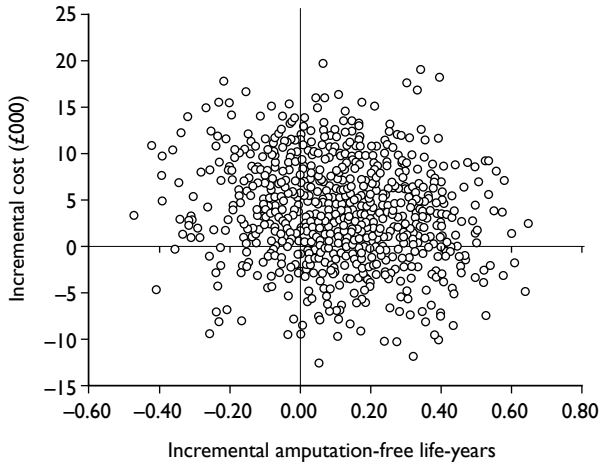
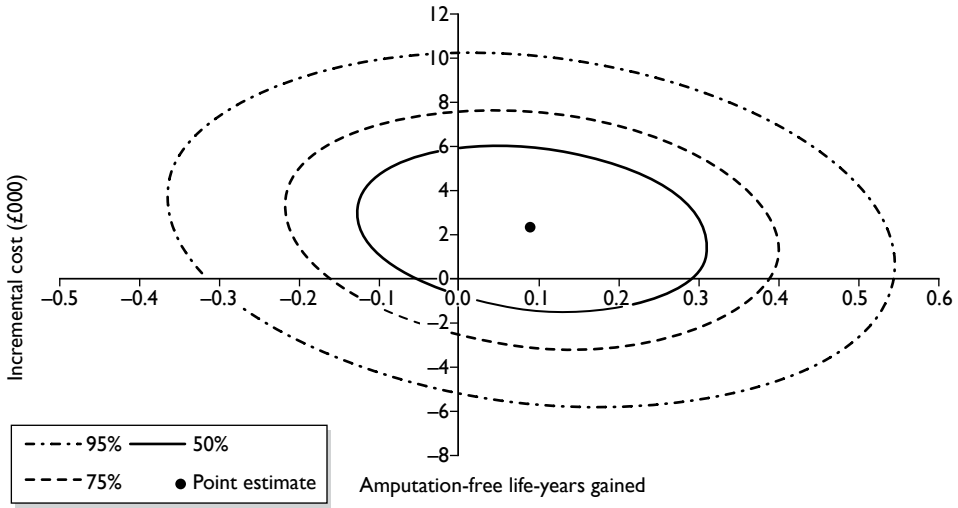
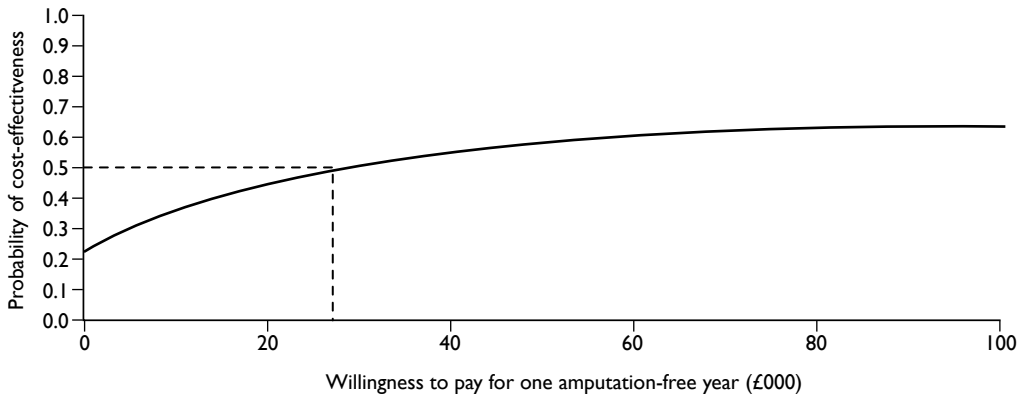


FIGURE 24 *Incremental costs and incremental amputation-free life-years calculated over 7 years (surgery versus angioplasty bootstrapped estimates).*





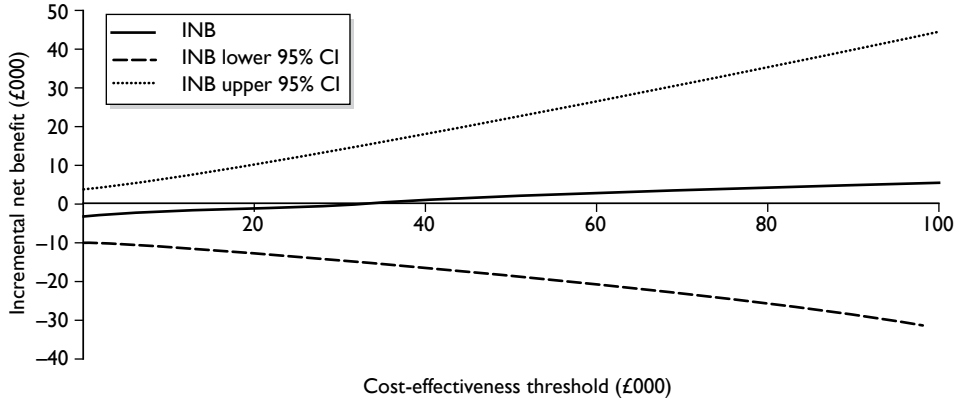


FIGURE 25 *Incremental net benefit of a surgery-first strategy. Cost per amputation-free life-year calculated over 7 years.*

Relationship between differences in cost and differences in overall absolute and quality-adjusted survival

Similarly, (Figures 26 and 27) incremental cost-effectiveness analyses can be undertaken in respect of OS (to 7 years) and quality-adjusted OS (to 3 years). As suggested by the point estimates, the cost-effectiveness of surgery compared with angioplasty is lower when these health end points are assessed. This is particularly the case when incremental costs of surgery are compared with the incremental gain in QALYs (calculated over 3 years only) where relatively large values have to be placed on an additional QALY before a surgery-first strategy could be regarded as a cost-effective use of resources. The confidence interval surrounding all values of cost-effectiveness also includes negative values reflecting the uncertainty and imprecision of the estimates and the relatively small incremental health gain when surgery is compared with angioplasty.

Discussion and conclusions

HRQoL

As expected, both the generic and disease-specific HRQoL of the BASIL trial cohort was very low at baseline.[67–71] No clinically significant differences between the two trial arms emerged across a range of generic and disease-specific HRQoL measures.[72,73] However, as suggested above, HRQoL data do have limitations and have to be interpreted with caution in the context of an understanding of the clinical realities for this group of high-risk and highly morbid patients.[74–77] The response rates were low (equally so in both trial arms) beyond 12 months; this is disappointing but perhaps to be expected in this patient population. Responders were more likely to have their trial leg intact and, presumably therefore, to exhibit higher levels of generic, but especially disease-specific, HRQoL.[78]

Although patients have a very low HRQoL before treatment, surgery and angioplasty have very similar effects on short-term gains in HRQoL, which appear to be sustained for at least 36 months following randomisation. This plateau effect may reflect the fact that the aggregate data are conflating two very different groups of patients: those who keep their legs and those who do not.[79–85]

As others have found,[86,87] the relative clinical and haemodynamic advantages and disadvantages of a surgery-based versus an angioplasty-based strategy for managing SLI due to infrainguinal disease may not be easily distinguishable by means of generic or disease-specific HRQoL.[88–95]

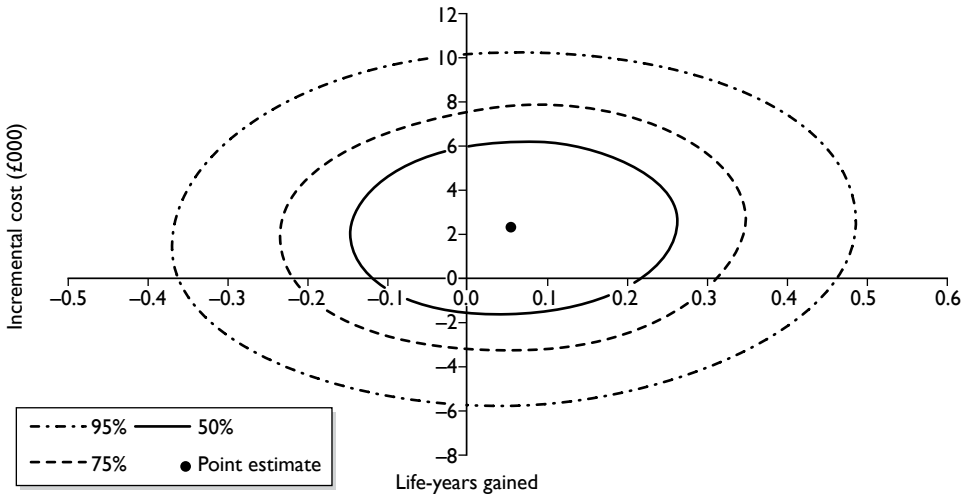
Costs

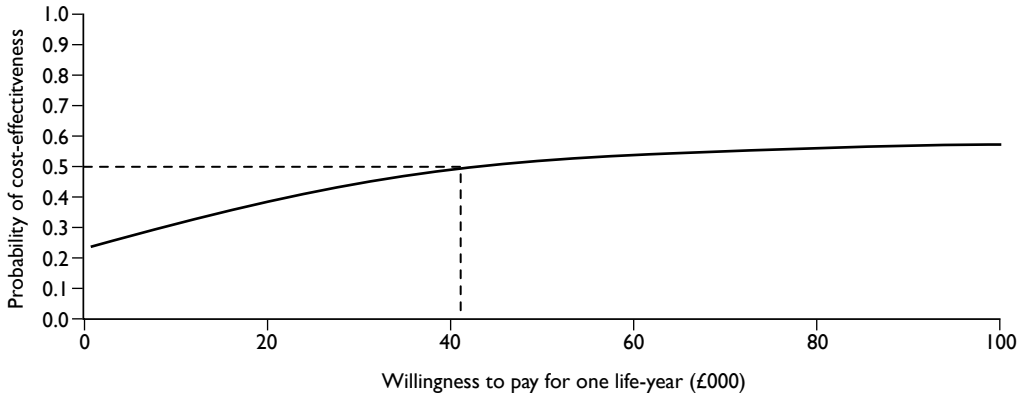
The hospital costs over the first year were approximately a third higher with a surgery-first than with an angioplasty-first strategy (see Chapter 2). Although the cost of the surgical procedure is significantly greater than that of an angioplasty, the main difference was related to the length of hospital stay, including the greater requirement for patients undergoing surgery to be cared for within an HDU or ITU environment.

As has been stressed, we were unable to quantify the costs associated with the use of health and social services outside hospital so our results underestimate some elements of the total costs of managing SLI;[96–98] for example, those arising from the rehabilitation of amputees. However, as the number and timing of amputations was broadly similar between the two trial arms, the relative cost differences are unlikely to be significantly different from zero. This assumes that amputees in both groups use roughly similar patterns of health and social services in non-hospital settings following the index hospitalisation episode.

We report within trial analyses on an intention-to-treat basis. We do not condition our economic analysis on survival probabilities (e.g. at 2 years) nor conduct a subgroup analysis of patients selected according to other characteristics which might have an impact on OS beyond 2 years. The pattern of cost-effectiveness would probably vary across different patient subgroups given the heterogeneous characteristics of patients and the criteria for patient selection and assignment to specific management strategies.

In principle, the within-trial analyses could be complemented by longer run (e.g. beyond 7 years) modelling or beyond-trial forecasting of costs and health effects. This would require information on the expected distribution of survival times, HRQoL and use of health services over a relatively long time horizon. Routinely generated information or observational data for patients with SLI would have to be carefully matched against the specific





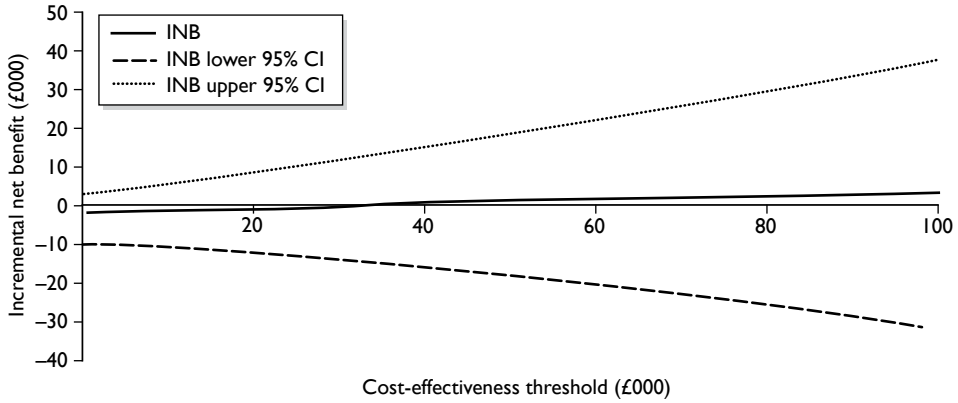


FIGURE 26 *Incremental net benefit of a surgery-first strategy. Cost per life-year calculated over 7 years.*

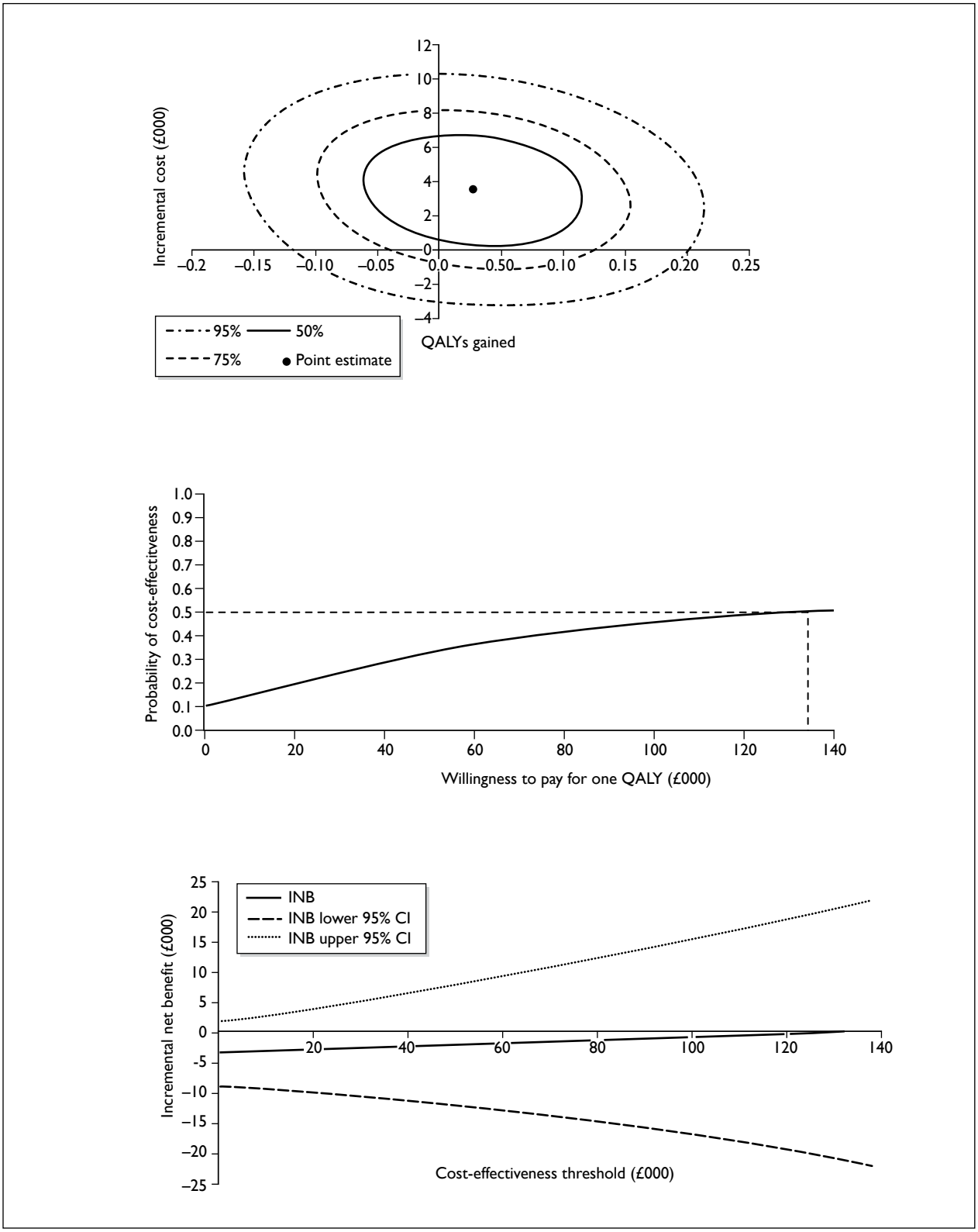


FIGURE 27 *Incremental net benefit of a surgery-first strategy. Cost per QALY calculated over 3 years.*

characteristics of our trial participants to ensure that the forecasting was valid and reliable. A naive model based on simple actuarial life tables and average resource use for patients in broadly similar age groups could be misleading and easily misinterpreted.

The costs estimated in this pragmatic vascular surgery trial accounted for the inpatient hospital spell(s) following randomisation up to 7 years. It reflected contemporary utilisation of hospital inpatient services by patients allocated to one of the strategies in BASIL. Although we believe our estimate of the differences in hospital costs between these alternative policies is robust, the absolute and relative differences are primarily a reflection of observed practice in the BASIL trial centres between 1999 and 2005 and the specific resource unit costs applied in our study.[48] The use of hospital resources and cumulative costs over 1 year are also broadly similar to recent reports that consider the distribution of costs over a longer time horizon.[96,97] When costs are measured in a more comprehensive way, capturing not only the initial episode of care but subsequent readmissions for (often) multiple operations and procedures, a more accurate estimate of the resource consequences of caring for patients presenting with SLI is obtained. Both resource use and cost will vary across different health-care systems and may change over time as novel interventions are adopted and a new pattern of service use is established. Our results should be interpreted carefully against the background of comparisons of resource use for a relatively small number of patients who present with SLI, undergo diagnostic imaging and are selected for some form of revascularisation. This has the inevitable effect of making inferences less precise and reliable than we would like. In addition to the standard problems encountered when comparing distributions estimated with a large degree of imprecision, we have the attendant problem of censoring, as we were unable to follow up patients beyond a relatively short period following randomisation.

This economic evaluation of these two strategies in patients presenting with SLI due to infrainguinal disease can be used to inform some of the arguments surrounding the advantages and disadvantages of each strategy. We provide estimates of cost-effectiveness that can be assessed against a range of WTP thresholds. These have recently drifted upwards toward £50,000 or more in the UK but even in this neighbourhood, it is correct to infer that both strategies are more or less equally cost-effective. This is not surprising given the closeness of the cost distributions and treatment effects measured in terms of the principal trial end points. Surgery does appear to have a significant positive impact on the distribution of hospital costs with (small) positive health effects. However, it is unlikely that the average net monetary benefit is significantly different from zero, as over a wide range of WTP thresholds there remains a substantial probability that surgery may in fact lead to an increase in costs with little and possibly negative effects on health.

However, cost-effectiveness of traditional alternatives to angioplasty or surgery for the majority of these patients is unknown. Less aggressive surgical or radiological interventions might prove attractive from a resource perspective but could also lead to higher morbidity and mortality risks. Amputation may offer a less expensive option (at least in terms of hospital costs) than either angioplasty or surgery because readmission is unlikely following discharge from the acute setting. However, once we factor in costs beyond the initial intervention[75,98,99] and take account of the preferences of patients and their families, it is far from clear whether amputation would be a more cost-effective approach compared with the SLI management strategies studied in the BASIL trial.

A clear and unambiguous guide to how clinical practice can be best influenced is difficult to identify when the costs and benefits of these alternative strategies are so evenly balanced. There are other important considerations that need to be introduced into the decision-making process, involving not only the preferences of individual patients but also surgeons and other health professionals who will need to agree on the relative merits of these management strategies. The choice and timing of interventions, once patients appreciate the likely effects on their health and perceptions of well-being, will require not only awareness of costs and benefits but careful and sensitive discussion.

Chapter 8

Delphi consensus study

Introduction

In the UK, over 20,000 patients are treated for SLI each year at an estimated cost of £1 billion.[100] Similar data are available for many other European countries.[1] The relative indications for bypass surgery and angioplasty remain controversial with strongly held and diametrically opposed views being expressed by surgical and radiological experts.[34,101–104] Two trials have suggested that surgery and angioplasty may achieve similar survival and limb salvage rates in certain patients. However, both trials were small and methodologically flawed and provide little or no evidence on which to base current treatment.[5,20] Clinicians' views are, therefore, almost entirely based upon personal experience, the nature of their training and the results of uncontrolled observational studies.

Many vascular surgeons believe that surgery is the treatment of choice for virtually all patients affected by SLI. However, angioplasty is increasingly used as a first-line treatment because surgery is associated with significant mortality, not all patients have a suitable vein for bypass and there is a lack of health-care resources and trained personnel to perform these demanding operations.[105] There are also a number of theoretical advantages to angioplasty: it may be safer, quicker, less expensive and may not prejudice subsequent surgical bypass if required.[105] On the other hand, the surgical bypass may provide a more complete and durable revascularisation of the limb. The Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL) trial is an ongoing UK-based, Health Technology Assessment funded, multicentre, RCT comparing the clinical and cost-effectiveness of a 'bypass-first' with an 'angioplasty-first' strategy in patients with SLI.[39] As described in the protocol (see Appendix 1) we undertook a Delphi consensus study to:

- examine the level of agreement among vascular surgeons and interventional radiologists with regard to the surgical and endovascular management of SLI
- establish a 'grey area of clinical equipoise' before the start of the BASIL trial.

Methods

Modified Delphi technique

The modified Delphi consensus method is an accepted means of quantifying the level of agreement among a group of medical 'experts'.[106,107] The technique has been applied to a wide range of clinical areas including interventions for vascular disease.[80,108] Briefly, a panel of 'experts' is asked to rate independently the appropriateness of each intervention for a range of hypothetical clinical scenarios. The median and range of these first-round responses are fed back to panellists so that each can see where their response lay in relation to those of their peers. Panellists are given the opportunity to amend their response in a second round by completing the questionnaire again. From these data the initial and final level of agreement, as well as the degree of convergence between the first and second rounds, can be quantified.

Panellists

At its inception, the BASIL trial was based in Scotland and the North-East of England. All the consultant vascular surgeons and interventional radiologists working in this geographical area had agreed to participate in the trial. The trial subsequently incorporated several other English centres. The Delphi consensus questionnaire was, therefore, sent to all 37 consultant vascular surgeons and 31 consultant interventional radiologists working in these areas/centres. Twenty (54%) surgeons and 17 (55%) radiologists (see Acknowledgements) provided complete and evaluable responses for both rounds.

Delphi questionnaire

Surgeons and radiologists were presented with 596 different hypothetical patient scenarios. Scenarios provided information regarding the anatomical extent of disease, whether the patients had rest pain only or had tissue loss (defined as ulceration and/or gangrene with or without rest pain) and whether or not a suitable vein for bypass was available.

Anatomical extent of disease

Panellists were presented with angiographic representations (Figure 28) depicting three main infrainguinal segments (superficial femoral artery, popliteal artery and crural arteries). Each segment was presented as having 'no disease', 'focal (< 10 cm) non-occlusive disease', 'diffuse (> 10 cm) non-occlusive disease', 'short (< 10 cm) occlusion' or 'long (> 10 cm) occlusion'. In disease scenarios that included a long occlusion of the crural arteries, participants were also asked to consider their response in the presence of a patent (with 'run-off') and occluded ('without run-off') pedal arch. Allowing for all possible disease combinations, this resulted in a total of 149 angiographic representations. We did initially intend to conduct the study with actual angiogram films. However, it became almost immediately apparent that it was going to be impossible to obtain angiograms of sufficient and, importantly, uniform quality that represented all the (very many) different combinations of disease. Furthermore, the copying and transportation of these films to all the panellists proved to be logistically and financially impossible.

Clinical severity of disease and suitable bypass

Participants were asked to consider each angiographic representation in the presence of rest pain only versus tissue loss (ulcer and/or gangrene). Panellists were asked to assume that all the patients' symptoms/signs were the result of arterial disease. It was the view of the Consensus group that the addition of ankle pressure would not be helpful.

Presence of vein

Participants were asked to consider each angiographic representation in the presence of a suitable vein for bypass versus no suitable vein. As

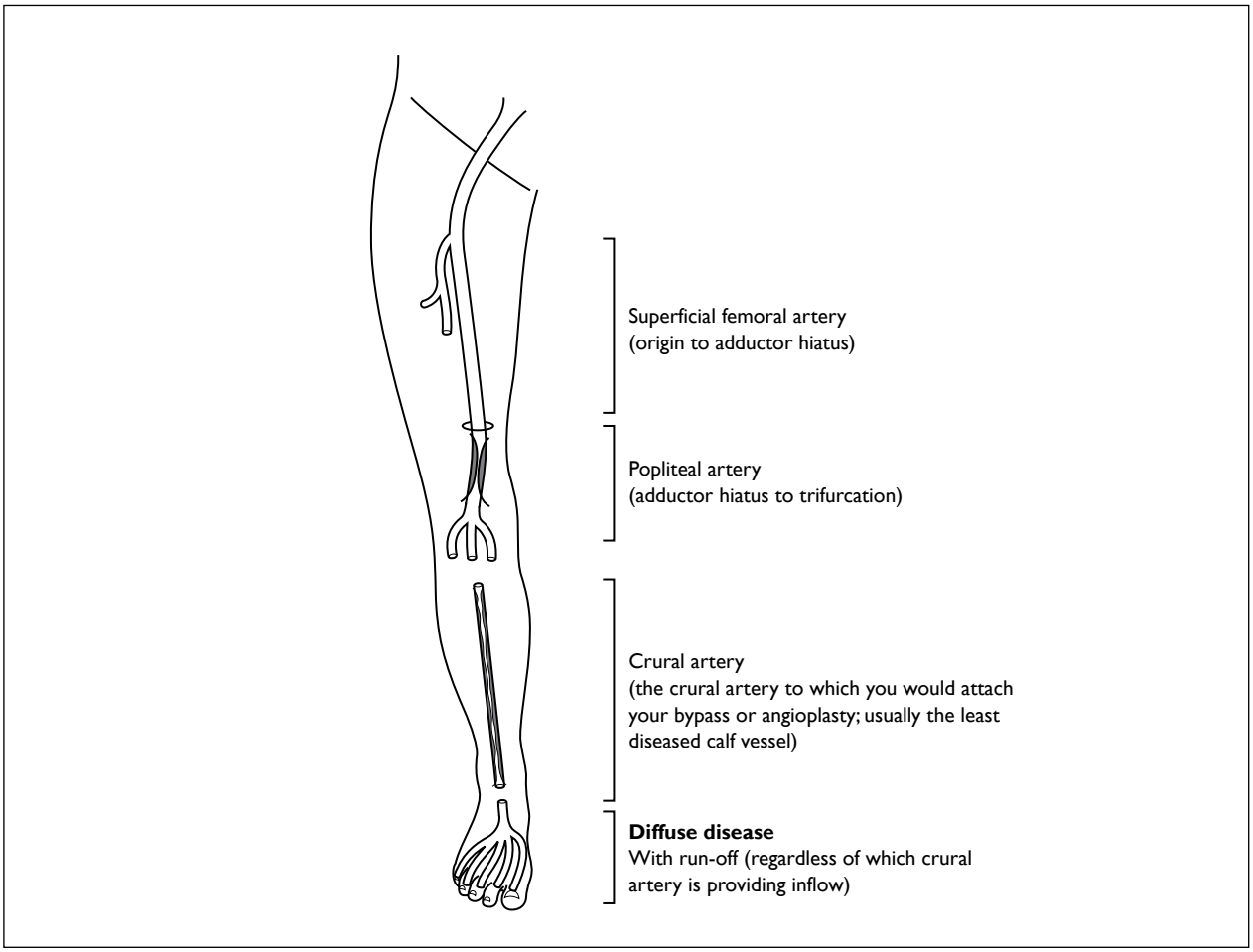


FIGURE 28 *Example of an angiographic representation used in the questionnaire.*

practice varies with regard to the relative use of veins other than the ipsilateral long saphenous vein and prosthetic grafts, the nature of the conduit to be used was not further prescribed.

Scoring

For each of the 596 scenarios, respondents were asked to score their preferred treatment option as follows:

- could only be treated by percutaneous transluminal angioplasty (PTA)
- could be treated by PTA or surgery but I strongly prefer PTA
- could be treated by PTA or surgery but I prefer PTA
- could be treated by PTA or surgery and I have no preference
- could be treated by PTA or surgery but I prefer surgery
- could be treated by PTA or surgery but I strongly prefer surgery
- could only be treated by surgery
- not amenable to revascularisation – primary amputation.

Assumptions

In formulating their responses, participants were asked to make four assumptions:

- There was no significant suprainguinal or profunda femoris artery disease.
- Medical therapy had failed such that revascularisation, by either surgery or PTA, or primary amputation were the only options.
- Apart from the information provided to them, there were no other contraindications to either surgery or PTA.
- The crural artery depicted was the least diseased of the three and so was likely to be the target artery for surgical or endovascular treatment.

TABLE 56 *Six agreement groups for Delphi questionnaire responses*

All responses fell within the range:	Agreement that
1–3	Angioplasty strongly preferred
2–4	Angioplasty preferred
3–5	No preference
4–6	Surgery preferred
5–7	Surgery strongly preferred
6–8	Surgery/amputation preferred

Most of the panellists found that it took 1–2 hours to complete each questionnaire.

Data analysis

To allow for direct comparison between rounds only responses received from the 20 surgeons and 17 radiologists who completed both rounds were considered. By convention, the highest 10% and lowest 10% of the responses were discarded as 'outliers'. The remaining responses were deemed to show 'agreement' if they fell within a three-point range and 'disagreement' if they did not. This resulted in six possible agreement groups as shown in Table 56.

The results were analysed for all respondents and for surgeons and radiologists only. Agreement was also assessed by means of the weighted kappa-statistic, which was calculated from a summary table of frequencies based upon the comparison of each possible pair of raters. As the numbers of observers and scenarios are large, these estimates are extremely precise, and confidence intervals are not presented. A kappa-value < 0.40 is defined as poor agreement. Equipoise was defined as existing when there was a consensus that both angioplasty and surgery would be equally clinically effective (three-point agreement for 3–5 'no preference') or where there was disagreement about the preferred treatment.

Results

Treatment preferences in round 1

In round one, there was little difference between the distribution of surgical and radiological responses, both of which were bimodal (Figure 29).

Both surgeons and radiologists thought primary amputation was indicated in approximately 9–10% of scenarios. Although both groups felt that surgery was preferred in the majority of scenarios (surgeons 46% and radiologists 48%), the strength of the preference for surgery was greater for the surgical group. By contrast, surgeons thought angioplasty was to be preferred in 38%, compared with 35% for radiologists, with the strength of the preference being very similar between the two groups. Surgeons and radiologists expressed no

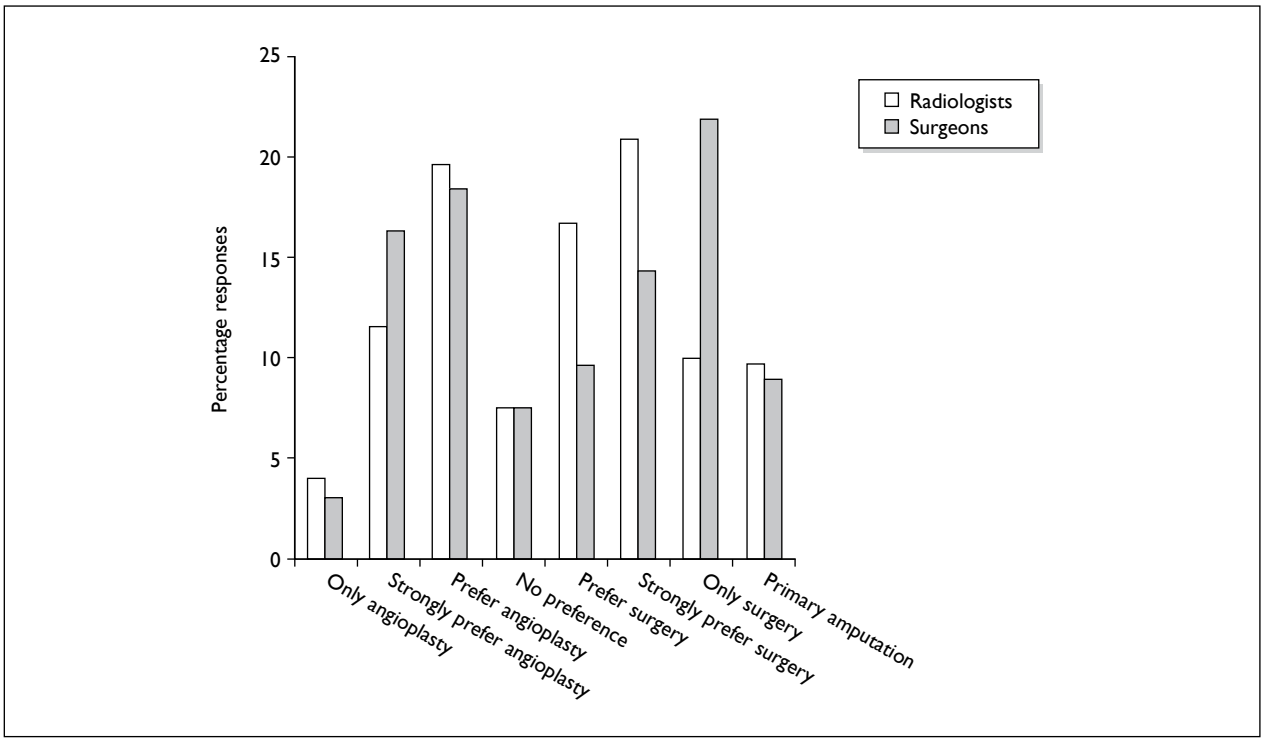


FIGURE 29 *Percentage of surgical and radiological responses in each category in round 1.*

preference for either treatment in 7.5%. It appears therefore that, in the great majority of scenarios, both surgeons and radiologists had moderate to strong preference for one or other treatment. However, with regard to the level of agreement as to which was the preferred treatment, when surgical and radiological responses were combined, the weighted kappa-statistic was 0.25. Although the weighted kappa was higher for radiologists (kappa = 0.29) than for surgeons (kappa = 0.21), all three kappa-values denote poor agreement.

Treatment preferences in round 2

Although individual respondents frequently changed their responses in round 2, overall there was little change in the distribution of surgical or radiological responses (Figure 30). Surgeons still felt that most scenarios warranted surgery but the strength of that preference diminished and there was some movement towards angioplasty by both groups. The proportion of scenarios thought to warrant primary amputation increased a little as did the proportion in which surgeons and radiologists expressed no preference for either treatment. When surgical and radiological responses were combined, the weighted kappa-statistic was 0.38, which was higher than in round 1 but still denotes poor agreement. The weighted kappa for radiologists rose to 0.45, denoting moderate agreement, but agreement among surgeons remained poor (kappa = 0.32).

Level of agreement and convergence between rounds

When the surgical and radiological responses were combined there was substantial disagreement in 484 (81%) of scenarios in round 1 and 401 (67%) in round 2 (Figure 31). This disagreement (Table 57) was greater among surgeons than radiologists in both round 1 (83% vs 65%) and round 2 (69% vs 42%). Although, because of their smaller number, one would expect a greater level of agreement among radiologists, this would not account for the large differences in the level of consensus observed between surgeons and radiologists. There was a better level of agreement among surgeons (kappa = 0.77) than radiologists (kappa = 0.61) between the first and second rounds. This was because, in round 2, radiologists were more likely than surgeons to change their score towards the group mean on the basis of feedback from round 1.

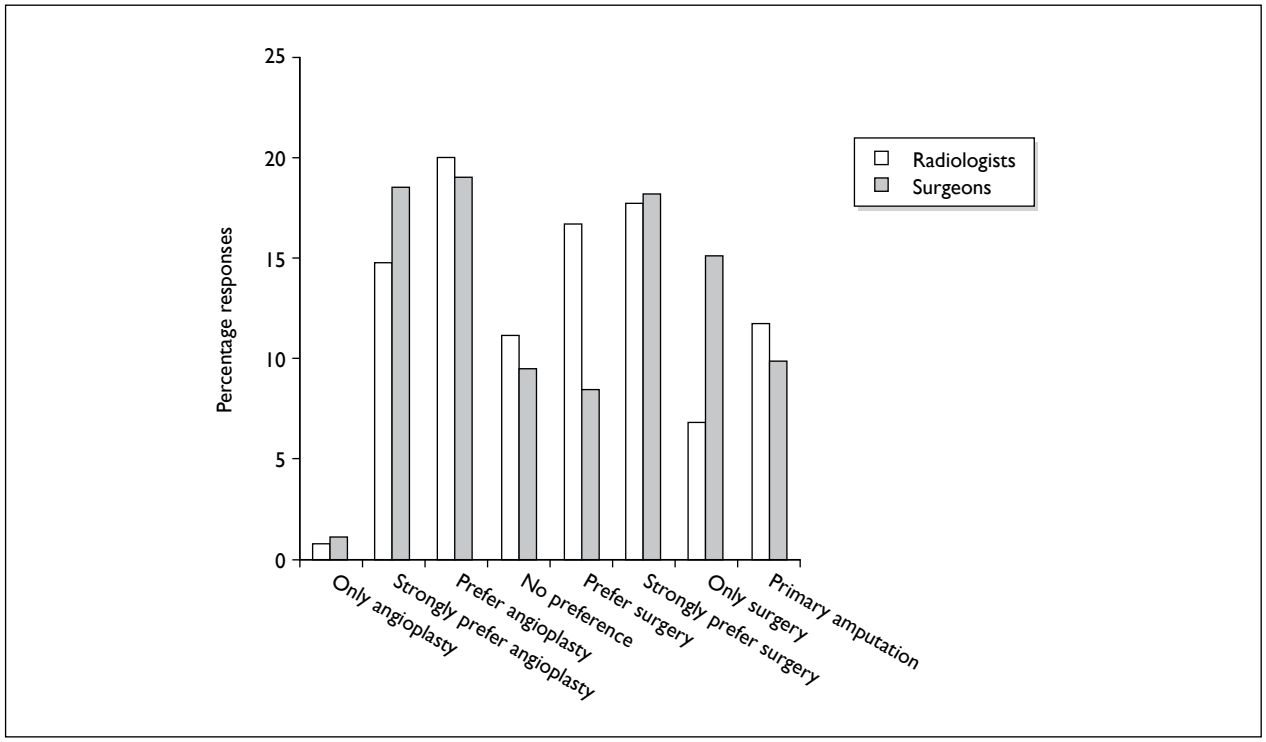


FIGURE 30 *Percentage of surgical and radiological responses in each category in round 2.*

'Grey area of clinical equipoise' for the BASIL trial

Equipoise was defined as existing when there was a consensus that both angioplasty and surgery would be equally clinically effective (three-point agreement for 3–5 'no preference') or where there was disagreement about the preferred treatment.

In round 1, 81% of scenarios fell into the grey area compared with 68% of scenarios in round 2 (Table 58). In both rounds, the grey area comprised largely scenarios in which there was disagreement rather than scenarios in which there was agreement that either treatment would be equally effective.

TABLE 57 *Number and percentage of disease scenarios falling into each three-point agreement and disagreement range for rounds 1 and 2 for surgeons only and radiologists only*

	Surgeons only				Radiologists only			
	Round 1		Round 2		Round 1		Round 2	
	n	%	*n*	%	*n*	%	*n*	%
123	25	4.2	62	10.4	45	7.6	93	15.6
234	32	5.4	96	16.1	74	12.4	136	22.8
345	0	0.0	1	0.2	22	3.7	72	12.1
456	0	0.0	5	0.8	32	5.4	61	10.2
567	46	7.7	68	11.4	77	12.9	86	14.4
678	21	3.5	36	6.0	21	3.5	50	8.4
Any agreement	103	17.3	187	31.4	210	35.2	343	57.6
Disagreement	493	82.7	409	68.6	386	64.8	253	42.4

Note that some response combinations would appear in the 'any agreement' line more than once. For example, if there is a two-point agreement of '23' this will appear in the '123' and '234' agreement categories.

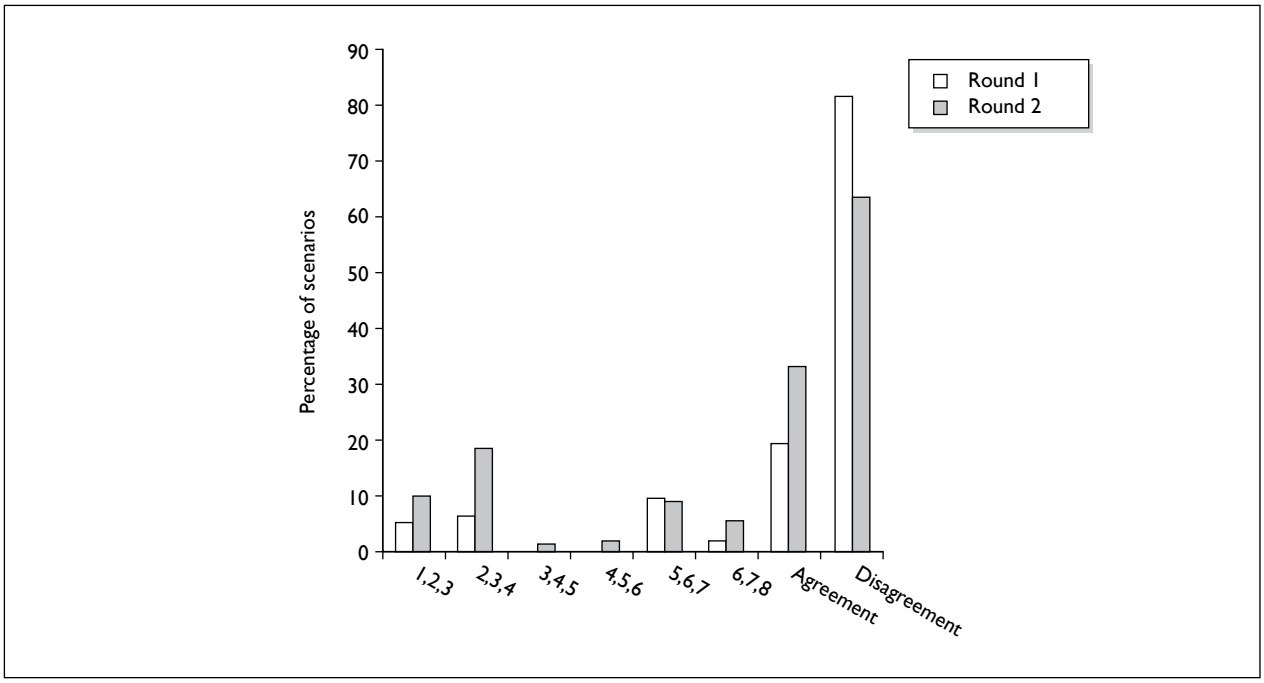


FIGURE 31 *Level of agreement and disagreement regarding the appropriateness of angioplasty or surgical bypass.*

Discussion and conclusions

The clinically important finding of the study is the very substantial level of disagreement between and among surgeons and radiologists with regard to the appropriateness of surgery or angioplasty for SLI over a wide range of clinical and angiographic severities of disease. Despite the fact that the information provided to the panellists was less complex than would be the case in the real clinical situation, in round 1 there was disagreement among surgeons in 83%, and among radiologists in 65%, of scenarios. Although there was some convergence of views in round 2 following feedback from peers, the level of disagreement was still 69% for surgeons and 42% for radiologists. This lack of consensus, which is reflected in the literature, stems from the absence of an evidence base and means that the same patient may receive entirely different treatment depending on which hospital they attend. Indeed, such is the lack of consensus that surgeons and radiologists working in the same institution might disagree fundamentally about which treatment option is most desirable, possible, or even ethical. While some would argue that a good result can be obtained in exactly the same patient using two completely different techniques, equivalence in terms of clinical effectiveness and cost-effectiveness is, in reality, unlikely and cannot be assumed in the absence of evidence. So it is our view that the very considerable and largely unexplained variation in practice demonstrated in this study is likely to disadvantage patients. Furthermore, it has major implications for the

TABLE 58 *'Grey area of clinical equipoise' for the BASIL trial*

		Agreement within '345' range (%)	Disagreement (%)	Total (%)
Round 1	Surgeons	0.0	82.7	82.7
	Radiologists	3.7	64.8	68.5
	Combined	0.0	81.2	81.2
Round 2	Surgeons	0.2	68.6	68.8
	Radiologists	12.1	42.4	54.5
	Combined	0.8	67.3	68.1

planning and use of health-service resources, referral pathways and, of course, surgical and interventional training. Although the present study has clearly demonstrated a large collective 'grey area of clinical equipoise', there is much less equipoise on the part of individual clinicians. The bimodal response distribution observed for surgeons and radiologists, and which changed relatively little between the two rounds (especially for surgeons), indicates that most clinicians have strong preferences as to how individual patients should be treated; despite a complete absence of level 1 evidence. Hopefully, recognition that current practice is not evidence-based, together with the results of this present study, will encourage the randomisation of patients into the BASIL trial within the UK. However, the difficulty of changing individual clinical opinion cannot be underestimated: 'sometimes wrong, but never in doubt'.

Chapter 9

Factors affecting the decision-making of surgeons and interventionalists – an extended Delphi study

Introduction

As described in Chapter 8, to define the level of agreement and disagreement among individual vascular surgeons and interventional radiologists with regard to the relative merits of surgery and angioplasty in patients with SLI, and to establish the breadth of the 'grey area of clinical equipoise' for the trial, we conducted a Delphi consensus study. This study indicated substantial levels of disagreement between and among surgeons and radiologists with regard to the appropriateness of surgery or angioplasty for SLI over a wide range of clinical and angiographic severities of disease.[35] Here we present a further, novel, more detailed statistical analysis of the data that seeks to determine the reasons for these differences in terms of the patients' clinical presentation and their angiographic pattern of disease.[37]

Methods

Overview

The Delphi methodology has been described in Chapter 8.

Statistical analysis

Multiple linear regression was used to determine which factors influenced treatment preference by surgeons and interventional radiologists. A data point was generated for each of the 596 scenarios. The mean response over all observers was used as the dependent variable. The six predictive factors (four angiographic, two clinical) considered were the extent of disease in the superficial femoral, popliteal and crural arteries, whether there was 'run-off' into the foot (in scenarios that included a long occlusion of the crural vessels), the presence of rest pain or tissue loss and the presence or absence of a suitable vein. Three different regression models are reported:

- A – main effects only with variables entered as ordinal variables
- B – main effects and interactions with variables entered as ordinal variables
- C – main effects with variables entered as nominal variables.

Stepwise regression was used; main effects and interactions entered and left the model at the 5% and 1% significance levels respectively. The stepwise procedure started with no variables in the model. Step 1 examined all one-variable models and the variable that was most predictive of the dependent variable, and was statistically significant at the 5% level, entered the model. Step 2 examined all two-variable models with one of the variables being the variable selected in Step 1. At each step, existing variables were examined, and if any main effects (if no interactions were in the model) or any interactions became non-significant at the 5% and 1% levels respectively, they were removed from the model. This process was continued until all the variables not already in the model were all non-significant at the 5% level.

When interactions were considered (Model B), first-order interaction terms were only allowed to enter into the model when both main effects had already been entered into the model. Main effects were not removed from the model if they became statistically non-significant in the model, unless the combined effect of the main effect and any interactions became non-significant. It was anticipated that factors might influence surgeons and radiologists in different ways, so separate models were constructed for all respondents, surgeons only, and radiologists only. Initially, the variables with more than two response categories (superficial femoral, popliteal and crural artery disease status) were entered into the model as ordinal variables. This assumed that any difference in observed response from one category to the next most severe was the same for all categories. So, for example, any difference in response/score from focal non-occlusive disease

(score 2) to diffuse non-occlusive disease (score 3) was equal to that from short occlusion (score 4) to long occlusion (score 5). Parameter estimates were used to obtain the predicted mean score for a particular disease scenario by multiplying the value for each factor by its parameter estimate, and then adding all these values to the intercept parameter estimate. The higher the predicted mean score, the more respondents favoured surgery. The standard error, a measure of variability of the parameter estimate, was also calculated. When using ordinal variables the importance of the various factors was examined using the t-statistic (the parameter estimate divided by its standard error). The higher the t-statistic, and the smaller the p-value, the more predictive the factor was of the response.

In Model C the disease states of the arteries were treated as categorical variables; in other words, this model did not assume that the observed change in response would be equal between successive states of disease in the arteries. For this model, analysis of variance was used to determine which factors predicted mean score. Least square means were calculated for each severity category for each factor. These give the mean response for a particular severity category for one factor assuming an average disease severity level for all the other factors in the model.

Results

Model A: analysis with ordinal variables and without interactions

When using the stepwise procedure without interactions, the final models for surgeons and radiologists were similar. All variables entered into the surgeons' model and only 'rest pain versus tissue loss' did not enter the radiologists' and all respondents' models. For this reason, full models, rather than the stepwise procedure are presented in Table 59.

All respondents

All the clinical and angiographic variables, except 'rest pain only versus tissue loss', enter the final model, which explains 67% of the total variability in mean response scores. Of the factors that are statistically significant, the presence or absence of a suitable vein is the least important (lowest t-statistic). Scenarios with tissue loss had a higher mean response (towards surgery or primary amputation), but it was not quite statistically significant ($p = 0.06$). However, it is worth re-emphasising that all the variables, except 'rest pain only versus tissue loss', have a significant (all $p < 0.0001$) and independent bearing on expressed treatment preferences. In summary, for the respondent group as a whole, an increased severity of disease in the three arterial segments (particularly the SFA), a lack of run-off into the foot, and the presence of a suitable vein all increase the mean response towards a surgical bypass or primary amputation.

Comparison of surgeons and radiologists

All the clinical and angiographic variables are statistically significant in the surgeons' model, and all except rest pain/tissue loss in the radiologists' model. The radiologists' model explained a higher percentage of the total variation in the mean score than for the surgeons' (68% and 62% respectively). Like surgeons, radiologists are most strongly influenced by the disease status of the superficial femoral and popliteal arteries. However, whereas surgeons are next most influenced by the status of the crural arteries, radiologists are more influenced by the run-off into the foot. Unlike surgeons, radiologists are not significantly influenced by whether the patient has rest pain only or tissue loss, although there is a trend towards angioplasty for those patients with rest pain only. It is interesting to note that radiologists' treatment decisions are just as strongly influenced by the presence of suitable vein as those of surgeons (t-statistics of 8.4 and 8.6 respectively).

Model B: analysis with ordinal variables and interactions

In the previous analysis, the effect sizes of different factors on the mean score are simply added. In this analysis, interactions are considered. For example, the effect size of run-off into the foot may depend upon whether there is a suitable vein or not. This type of analysis may be a more accurate reflection of real clinical decision-making, which usually involves weighing the effects of several different factors against each other.

All respondents

When interactions are considered for the group as a whole, the model becomes considerably more complex (Table 60).

Perhaps surprisingly, therefore, the model still only explains 70% of the total variation in the mean scores, a small increase over the model without interactions. However, the introduction of interactions does begin to demonstrate the

TABLE 59 *Multiple linear regression comparing the factors that influenced surgeon and radiologist treatment preferences (ordinal variables and no interactions)*

Variable	Parameter estimate (PE)	Standard error (SE)	*t* (PE/SE)	*p*-value
All respondents				
Superficial femoral artery	0.44	0.02	21.5	<0.001
Popliteal artery	0.30	0.02	14.6	<0.001
Run-off into foot	0.98	0.09	11.0	<0.001
Crural arteries	0.23	0.02	10.4	<0.001
Suitable vein or not	0.51	0.06	8.9	<0.001
Rest pain vs tissue loss	–0.11	0.06	–1.9	0.0604
Intercept	1.37	0.12	11.1	<0.001
Surgeons only				
Superficial femoral artery	0.42	0.02	19.2	<0.001
Popliteal artery	0.32	0.02	14.4	<0.001
Crural arteries	0.22	0.02	9.3	<0.001
Run-off into foot	0.84	0.10	8.9	<0.001
Suitable vein or not	0.52	0.06	8.4	<0.001
Rest pain vs tissue loss	–0.14	0.06	–2.3	0.0229
Intercept	1.51	0.13	11.5	<0.001
Radiologists only				
Superficial femoral artery	0.47	0.02	22.3	<0.001
Popliteal artery	0.28	0.02	13.5	<0.001
Run-off into foot	1.14	0.09	12.5	<0.001
Crural arteries	0.25	0.02	10.8	<0.001
Suitable vein or not	0.51	0.06	8.6	<0.001
Rest pain vs tissue loss	–0.07	0.06	–1.2	0.2238
Intercept	1.22	0.13	9.6	<0.001

complexity of the decision-making process. With most of the interaction terms, because their parameter estimates are negative, an increase in the severity of (particularly SFA) disease does not lead to as great an increase in mean response score as might be expected from the additive model. In other words, increasing severity of crural disease, the presence of suitable vein and the lack of run-off in to the foot increase the mean towards surgery, but the respondents' enthusiasm for surgery is dampened in comparison to that anticipated if the effects of interaction terms had not been considered. This may be largely the result of the surgical, as opposed to the radiological, response (see below). By contrast, the parameter estimate for the interaction term 'crural*vein' is positive; that is, the presence of suitable vein increases the enthusiasm for surgical bypass as the severity of crural disease increases. Specifically, in the absence of a suitable vein, the increase in mean score (towards surgical preference) for a two-point increase in the severity of disease in the crural arteries would be 0.94 (0.47 × 2). However, in the presence of suitable vein it would be 1.74 [(0.47 × 2) + 0.56 + (0.12 × 2)].

Comparison of surgeons and radiologists

When interactions are considered the model explains 68% and 71% of the total variation in the mean scores for surgeons and radiologists respectively, which represents a small increase over the model without interactions. For the surgeons' model, 'Rest pain versus tissue loss' is in the model, even though it is not significant itself (p = 0.84), because an interaction containing this main effect (run-off*pain/tissue loss) is statistically

TABLE 60 *Stepwise linear regression comparing the factors that influenced surgeon and radiologist treatment preferences (ordinal variables and interactions)*

Variable	Parameter estimate (PE)	Standard error (SE)	*t* (PE/SE)	*p*-value
All respondents				
Superficial femoral artery	0.70	0.06	12.8	<0.001
Popliteal artery	0.45	0.05	9.3	<0.001
Run-off into foot	1.83	0.22	8.4	<0.001
Crural arteries	0.47	0.07	6.8	<0.001
Suitable vein or not	0.56	0.19	3.0	0.0027
Run-off*vein	–0.76	0.17	–4.5	<0.001
SFA*crural	–0.05	0.02	–3.5	0.0005
Popliteal*crural	–0.04	0.01	–3.3	0.0011
Crural*vein	0.12	0.04	2.8	0.0058
SFA*vein	–0.10	0.04	–2.7	0.0078
SFA*run-off	–0.16	0.06	–2.6	0.0097
Intercept	0.21	0.25	0.9	0.3917
Surgeons only				
Superficial femoral artery	0.72	0.06	12.8	<0.0001
Popliteal artery	0.54	0.05	10.8	<0.0001
Run-off into foot	2.11	0.23	9.1	<0.0001
Crural arteries	0.61	0.07	8.9	<0.0001
Suitable vein or not	0.90	0.14	6.6	<0.0001
Rest pain vs tissue loss	–0.01	0.06	0.2	0.8429
Run-off*pain/tissue loss	–0.77	0.15	–5.1	<0.0001
Popliteal*crural	0.07	0.01	–4.8	<0.0001
SFA*crural	–0.06	0.02	–3.9	<0.0001
SFA*run-off	–0.23	0.06	–3.7	0.0002
Run-off*vein	–0.40	0.15	–2.7	0.0083
SFA*vein	–0.10	0.04	–2.6	0.0094
Intercept	–0.17	0.25	–0.7	0.4924
Radiologists only				
Popliteal artery	0.29	0.02	14.1	<0.0001
Run-off into foot	1.62	0.13	12.9	<0.0001
Superficial femoral artery	0.65	0.05	12.8	<0.0001
Crural arteries	0.34	0.05	6.5	<0.0001
Suitable vein or not	0.20	0.15	1.3	0.1826
Run-off* vein	–0.96	0.18	–5.4	<0.0001
SFS* crural	–0.05	0.01	–3.8	<0.0001
Crural*vein	0.14	0.05	3.2	0.0015
Intercept	0.79	0.20	4.0	<0.0001

significant. This also applies to the radiologists' model for vein. In general, the radiology model is less complex than the surgical model with fewer statistically significant interactions. As before, 'rest pain versus tissue loss' does not impact upon treatment preference for the radiologists. Whereas surgical treatment preference is strongly influenced by the presence of vein ($t = 6.6$), this is not the case with the radiologists ($t = 1.3$, $p = 0.18$). Interestingly, the significant interactions differed between surgeons and radiologists with the two groups only sharing two statistically significant interaction terms; namely; 'SFA*crural' and 'run-off*vein'. As noted above, in the group as a whole, the presence of crural disease, the presence of suitable vein and the lack of run-off into the foot all reduced the mean scores (indicating a lower preference towards surgery) as SFA disease severity increased when this was compared with the additive model. These three interaction terms ('SFA*crural', 'SFA*vein' and 'SFA*run-off') are also present in the surgical group but not, with the exception of 'SFA*crural', in the radiology group. It would appear that the combination of these adverse factors makes surgeons favour surgery, but not as much as anticipated if the factors were considered separately. By contrast, radiologists do not appear to view the likely failure of surgical bypass as an indication for angioplasty.

Model C: analysis with categorical variables and without interactions

All respondents

When arterial status is entered as a categorical variable, so that a linear relationship between response and level of disease is no longer assumed, the final model is able to explain 86% of response variability. All variables are statistically significant ($p < 0.0001$) including 'rest pain only versus tissue loss' ($p = 0.005$).

Assuming an average value for all other factors in the model, the difference in mean score between a patient with a normal SFA (least square mean = 4.30) and one with a long occlusion of the SFA (least square mean = 6.29) is 1.99 (Table 61). In other words, a long SFA occlusion results in a stronger preference for surgical bypass regardless of the other angiographic and clinical factors. Furthermore, an SFA with diffuse non-occlusive disease (least square mean 5.34) is thought to be less amenable to angioplasty than an SFA with a short occlusion (least square mean 4.60). The presence of suitable vein, a lack of run-off into the foot and the presence of tissue loss all significantly increase the preference for surgery.

Comparison of surgeons and radiologists

The models explain 81% and 87% of the total variability for surgeons and radiologists, respectively (Table 62). Unlike the surgeons, 'rest pain versus tissue loss' does not significantly influence treatment preferences ($p = 0.06$ for radiologists compared with $p = 0.002$ for surgeons); all other variables were statistically significant ($p < 0.0001$). When compared with radiologists, surgeons appear more likely than radiologists to recommend angioplasty in patients with diffuse non-occlusive disease, whether it is in the superficial femoral, popliteal or crural arteries. Radiologists are more inclined towards surgery in scenarios with lack of run-off into the foot than surgeons.

Discussion and conclusions

Severe limb ischaemia is an increasingly prevalent condition, associated with high levels of morbidity and mortality, and places huge clinical and financial burdens on health care and social services.[12] Many vascular surgeons believe that the treatment of choice for all patients is femorodistal bypass with autologous vein. However, in the UK, angioplasty is increasingly used as a first-line treatment because surgery is associated with significant morbidity and mortality, not all patients have a suitable vein for use as a conduit, graft patency rates may be disappointing, and there is a lack of health-care resources and personnel to perform the necessary operations. There are also a number of theoretical advantages to angioplasty; it may be safer, quicker, can be repeated, is possibly less expensive and may not prejudice surgical bypass if it is unsuccessful. Two small and imperfect RCTs have suggested that in a proportion of patients angioplasty can lead to limb salvage rates equivalent to surgical bypass.[13,14] These data and the increasing experience with angioplasty for SLI within the UK provide the scientific rationale and ethical basis upon which the BASIL trial rests. Furthermore, this Delphi consensus study has revealed very substantial levels of disagreement between and among surgeons and radiologists as to what constitutes the optimal treatment of SLI. Panellists disagreed about the appropriateness of treatment by angioplasty, surgery or bypass surgery in 81% of the scenarios in round 1 and 67% in round 2. Disagreement was greater among surgeons than radiologists in both round 1 (83%

TABLE 61 *Multiple linear regression comparing the factors that influenced surgeon and radiologist treatment preferences (categorical variables without interactions)*

		Least square means (standard error)		
Factor	**Level of disease**	**All**	**Surgeons**	**Radiologists**
Superficial femoral artery	No disease	4.30 (0.05)	4.39 (0.06)	4.19 (0.05)
	Focal non-occlusive	4.18 (0.05)	4.15 (0.06)	4.21 (0.05)
	Diffuse non-occlusive	5.34 (0.05)	5.21 (0.06)	5.50 (0.05)
	Short occlusion	4.60 (0.05)	4.57 (0.06)	4.62 (0.05)
	Long occlusion	6.29 (0.05)	6.25 (0.06)	6.32 (0.05)
Popliteal artery	No disease	4.41 (0.05)	4.40 (0.06)	4.43 (0.05)
	Focal non-occlusive	4.59 (0.05)	4.54 (0.06)	4.65 (0.05)
	Diffuse non-occlusive	5.05 (0.05)	4.96 (0.06)	5.15 (0.05)
	Short occlusion	4.90 (0.05)	4.89 (0.06)	4.91 (0.05)
	Long occlusion	5.75 (0.05)	5.78 (0.06)	5.71 (0.05)
Crural arteries	No disease	4.55 (0.06)	4.58 (0.07)	4.51 (0.06)
	Focal non-occlusive	4.61 (0.06)	4.62 (0.07)	4.60 (0.06)
	Diffuse non-occlusive	5.06 (0.06)	4.92 (0.07)	5.21 (0.06)
	Short occlusion	4.96 (0.06)	4.94 (0.07)	4.99 (0.06)
	Long occlusion	5.52 (0.03)	5.51 (0.04)	5.54 (0.03)
Vein	No suitable vein	4.68 (0.04)	4.66 (0.04)	4.71 (0.04)
	Suitable vein	5.20 (0.04)	5.17 (0.04)	5.23 (0.04)
Run-off	With run-off into foot	4.51 (0.02)	4.57 (0.02)	4.44 (0.02)
	Without run-off into foot	5.37 (0.06)	5.26 (0.07)	5.50 (0.06)
Rest pain vs tissue loss	Tissue loss	4.99 (0.04)	4.98 (0.04)	5.00 (0.04)
	Rest pain	4.89 (0.04)	4.84 (0.04)	4.93 (0.04)

vs 65%) and round 2 (69% vs 42%). These data also demonstrate a broad 'grey area of clinical equipoise' for the trial and reflect the controversy found in the literature.[8]

The aim of the present study is to extend the findings of the Delphi study by examining in detail the factors influencing the treatment of SLI by vascular surgeons and interventional radiologists as reflected in their responses to the first round of the Delphi process. In particular, we wished to use statistical modelling to determine the degree of unexplained response variability and to examine differences between vascular surgeons and radiologists.

The complexity of the decision-making process is readily apparent; despite the fact that the respondents were provided with a much simpler data set than would be the case in 'real life'. First, the angiographic representations could not, of course, reproduce the many hundreds of different disease patterns seen on angiography. Second, the clinical information was limited to two dichotomous

TABLE 62 *Percentage of total variability in mean response scores explained by each of the statistical models for all respondents, surgeons only and radiologists only*

	All respondents	**Surgeons only**	**Radiologists only**
Model A: ordinal variables, no interactions	67%	62%	68%
Model B: ordinal variables, with interactions	70%	68%	71%
Model C: categorical variables, no interactions	86%	81%	87%

variables; namely, 'rest pain only versus tissue loss' and 'suitable vein versus no vein'. Of course, in reality, veins exhibit a wide spectrum of quality from excellent to poor. Third, participants were asked to make a number of assumptions that should have made decision-making easier. For example, they could assume that there was no significant suprainguinal disease, the patients were fit for either treatment and that continued medical treatment was not an option. Table 62 compares percentage variance explained by the models investigated in this simplified scenario. When variables were considered as ordinal data there was a slight reduction in the unexplained variability when interactions were considered. However, when variables were treated as categorical data, the unexplained variability fell from 33% to 14%. The remaining variability to some extent reflects higher order interactions as well as disagreement among and between participants.

The orders of importance of predictors of mean response are the same in both ordinal models for all respondents (SFA disease, popliteal disease, run-off into the foot, crural disease and presence of vein). However, when surgeons' and radiologists' responses are considered separately, the order of importance of predictors varies substantially. The surgeons' models are more complex, but explained less of the response variability. This suggests that surgeons may take a wider range of variables into consideration when forming their view. In general, surgeons are more likely to favour surgical bypass as disease severity, particularly in the SFA, increases. However, the addition of interaction terms demonstrated that surgical enthusiasm for bypass was significantly dampened by the presence of crural disease, the absence of run-off into the foot and a lack of suitable vein. In other words, when the whole picture suggested that surgical bypass was likely to be associated with limited patency, surgeons still preferred surgery to angioplasty but less than would be anticipated from the additive model. Perhaps not surprisingly, radiologists did not share surgeons' enthusiasm for angioplasty in these circumstances.

One interpretation of the interaction data, which has resonance with clinical experience, is that when surgeons feel that bypass is unlikely to be successful they often ask their radiological colleagues to perform 'salvage' angioplasty on the basis that it is unlikely to harm the patient, the alternative is likely to be amputation, and it might be beneficial. While this approach is no doubt well intentioned, it does lead to difficulties in interpreting the available data in the literature, not to mention possibly being a significant misuse of health-service resources. If a unit's policy is to perform angioplasty only when bypass is likely to fail then the results are likely to be poor and confidence in the technique will be low. By contrast, in those units that view angioplasty as a first-line treatment, results are likely to be better, resulting in more confidence in angioplasty.

When variables were entered as categorical data the use of least square means indicated that radiologists felt more confident about tackling focal, as opposed to diffuse, disease. Somewhat surprisingly, they appeared to be almost as confident about treating crural as SFA disease. Few radiologists appeared enthusiastic to attempt full-length recanalisation of the SFA, possibly because most radiologists do not practise, or have limited experience with, the subintimal technique. In general, for any given severity and extent of disease, radiologists seemed more enthusiastic about surgical bypass than surgeons, whether or not there was suitable vein and whether or not the patients had rest only or tissue loss. This is perhaps surprising given that all the radiological respondents were highly experienced vascular interventionalists. These data may reflect radiologists' lack of confidence in angioplasty for SLI borne of poor experience with 'salvage angioplasty', a lesser appreciation of the advantages of vein, and possibly an overoptimistic view of the results of prosthetic femorocrural bypass.

Taken in conjunction with the results of the Delphi process these data confirm that there remains considerable disagreement among and between surgeons and radiologists with regard to the relative merits of angioplasty and bypass in the treatment of SLI. Present data indicate that part of this disagreement relates to the fact that surgeons and radiologists view the risks and benefits of their own, and their counterparts', treatment modality differently in the context of a similar angiographic pattern of disease and clinical features. This re-emphasises the need for joint surgical and radiological decision-making and the need for excellent communication so that colleagues are not working at cross-purposes or with misconceptions. Present data suggest that certain surgeons believe that if surgical bypass is unattractive then angioplasty should be attempted, even though it is also likely to be unsuccessful, because there is nothing to lose by trying. On the other hand, certain radiologists will take on very

extensive disease in the belief that, even if it fails, the procedure can be repeated and that angioplasty does not prejudice the outcome of subsequent surgical bypass should it be necessary. It is unlikely that either of these extreme views represents the most clinically and cost-effective way of using these two complementary, not competing, treatment modalities. These issues can only be settled within the confines of an RCT.

Chapter 10

Discussion: strengths and weaknesses of the trial

Background to trial

The UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (www.hta.ac.uk/) invited tenders for a trial to compare surgical and endovascular approaches to the treatment of lower limb-threatening ischaemia in 1996; our group was fortunate enough to be chosen to design and run the trial. The perceived need for such a trial was borne out of growing concerns regarding the lack of RCT evidence in the field and the trend towards angioplasty, and away from surgery, in the absence of any supporting controlled data.

It is striking that more than 10 years later the BASIL trial remains the only RCT to have addressed this question. Most, if not all, of the other studies that have been published over that time have continued to exhibit one or more of the serious methodological limitations that originally prompted the commissioning of the BASIL trial in the late 1990s. Specifically, these other studies have often been retrospective,[109–111] single-centre, single-surgeon, small,[112,113] mixing patients with claudication and SLI,[112,114,115] mixing together aortoiliac and infrainguinal disease,[116] providing only short[112,115] and/or incomplete[111] follow-up, excluding technical failures,[117] and using non-clinical 'surrogate' end points.[118] Despite these methodological problems, the paucity of good quality data, and concerns over durability,[119] especially in patients with more advanced disease,[120] certain review articles continue to strongly advocate an endovascular rather than a surgical approach to SLI as the 'standard of care' for the majority of patients with lower limb ischaemia.[121,122]

The BASIL trial aimed to determine whether in patients with SLI due to infrainguinal arterial disease a 'bypass-surgery-first' or a 'balloon-angioplasty-first' revascularisation strategy was associated with a better outcome in terms of AFS and OS, HRQoL and use of hospital resources.

When comparing open surgery with minimally invasive (endovascular) alternatives, triallists often find themselves trying to weigh the relative merits of reductions in short-term mortality and morbidity against a possible lack of effectiveness, especially in the longer term (lack of durability). The clinical dilemma as to whether to subject a usually elderly and unfit patient with SLI to a lesser, arguably safer treatment now (such as balloon angioplasty) at the risk of possibly compromising their long-term outcomes (amputation, death) can be difficult to analyse statistically within the confines of an RCT.

As presented in Chapters 2, 3 and 4 and discussed below, the correct interpretation of the data and so the appropriate treatment for each individual patient will depend to a large extent upon the timescale under consideration.

The main findings of the final intention-to-treat analysis

Looking at the BASIL trial cohort and the follow-up period as a whole there was no significant difference in AFS and OS between the two strategies. That might be viewed by some as a negative result and of no great interest. However, such a perspective overlooks the key purpose of, and outcomes from, the trial and the time-dependent survival analysis pre-specified in the statistical plan.

In the short term, bypass surgery is non-significantly more hazardous than balloon angioplasty as well as more expensive; so, given a 1- to 2-year perspective, a balloon-angioplasty-first strategy appears advisable. However in the longer term, balloon angioplasty is significantly more hazardous in terms of OS than bypass surgery. So, for those patients in whom a longer-term perspective is appropriate, a bypass-surgery-first strategy appears advisable; especially as in the longer term there is probably no significant difference in HRQoL or costs between the two treatments.

Patients who survived for 2 years and who were initially randomised to bypass surgery gained a significant c. 7 months of additional life expectancy and an additional non-significant c. 6 months of amputation-free life expectancy, over the subsequent follow-up period when compared with those randomised to balloon angioplasty. Although these may not seem large differences, in the context of a condition with a very poor overall prognosis (worse than many common malignancies), affected patients and physicians may be likely to view them as meaningful gains in life and limb.

Initial perusal of trial data suggests that factors that may possibly explain the long-term survival benefit for bypass surgery include the quality of medical care and follow-up, enrolment in graft surveillance programmes and a more complete and durable revascularisation as judged by haemodynamic indices, relief of symptoms and healing of minor amputations. However, at the present time this remains mere (although we think reasonable) speculation. The influence of these factors on outcomes is being analysed and will be the subject of further separate reports. One obvious possible explanation for the long-term survival benefit after bypass surgery might have been the survival of the fitter patients into the second period. However, the fact that the observed differences in OS in the period beyond 2 years were not attenuated by adjustment for covariates found to be predictive of outcome at baseline (Chapter 4) makes this explanation unlikely.

Severe limb ischaemia imposes serious health and economic burdens in all developed, and an increasing number of developing, countries. As a result of uncontrolled tobacco consumption and the increasing prevalence of diabetes across the world, the global burden of SLI is likely to grow significantly in the future. As with any common and serious condition it is imperative that, where possible, management decisions are based on level 1 evidence. The BASIL trial is the only source of 'level 1' evidence in this field and suggests that a bypass-surgery-first strategy should normally be regarded as the treatment of choice for the c. 75% of SLI patients who are estimated likely to live longer than 2 years. Those unlikely to survive 2 years would seem better served by balloon angioplasty in most cases.

Improving the prognosis for severe limb ischaemia

One possible, although somewhat 'glass-half-empty', conclusion that might be drawn from the BASIL trial, and other multicentre/population-based reports that reflect SLI outcomes across a whole health economy, is that the prognosis for SLI patients is bleak, almost regardless of what treatment is offered. What might be done differently going forward to try to improve this somewhat dismal overall outlook?

Medical therapy

The BASIL trial has reported disappointingly low levels of 'best medical therapy' (e.g. antiplatelet agents, lipid-lowering therapy) at the time patients were referred to vascular services. It would be comforting to think that it was a historical problem, now resolved, which simply reflected the timing of the recruitment period (1999–2004). However, currently available data clearly show that this is not the case; nor is it a phenomenon restricted to the UK health-care system. More recent data from the UK[123] and North America show that there is still very considerable room for improvement when it comes to implementing evidence-based best medical therapy[124,125] and, in particular, lipid-lowering treatment[124,126–128] in patients with peripheral arterial disease generally and those (highest-risk) patients with SLI/CLI, specifically. Such treatment will almost certainly increase OS and improve the results of surgical and endovascular interventions[129–131] at relatively little additional cost. This must surely be the highest priority for the global vascular community.

Bypass surgery outcomes

If physicians are going to be persuaded to take note of the BASIL trial data and recommendations in their everyday clinical decision-making, then they will need to be persuaded that the results of BASIL reflect the current 'standard of care'.[132,133] The problem is that the BASIL trial data set is not easily comparable against other data available in the literature because:

- multicentre data are limited
- there are no other RCTs available for meta-analysis
- of the particular characteristics of the patients eligible for, and so admitted to, the BASIL trial

(they had to be suitable for angioplasty and surgery) – this is discussed below.

Currently, the largest and best data set of vein bypass surgery for CLI comes from the PREVENT III trial of a novel drug (edifoligide), which was hypothesised to reduce vein graft failure by reducing restenosis. Although the drug was not shown to be effective, the trial has provided prospectively gathered, high-quality data on 1404 bypass surgery procedures undertaken in more than 80 North American centres between 2001 and 2003. However, unlike BASIL, only 'excised' vein grafts were undertaken (no prosthetic or 'in situ' grafts were included) and the follow-up was rather short at only 12 months. Furthermore, because of the hypothesis being tested[133] the trial protocol mandated an especially intensive graft surveillance and reintervention programme. Nevertheless, reported short-term outcomes (to 12 months) for comparable PREVENT III and BASIL trial patients were very similar. Rates of AFS and OS in BASIL are also similar to those reported by others around the same period,[134,135] so it would seem that the bypass surgery outcomes reported in BASIL are representative of what can reasonably be achieved in this type of patient across the health economies of most developed countries. However, we accept that physicians in certain 'centres of excellence' may continue to believe that their own results are substantially better that those usually reported from multicentre and registry studies.

It has been suggested that the BASIL trial should have specified a standard follow-up protocol which should have included (at least for the bypass grafts) mandatory duplex ultrasound-based graft surveillance and reintervention when certain haemodynamic criteria were met.[136–138] This approach was not regarded as 'standard of care' in the UK at the time the trial was designed. In fact, even today, although some form of graft surveillance seems intuitively beneficial, the only RCT to examine this controversial area did not show any clinical or cost-benefit from routine duplex-based surveillance.[88]

Angioplasty outcomes

The BASIL trial has been criticised for the very low utilisation of stents (nine cases). However, stenting of infrainguinal arteries was not regarded as standard of care in the UK at the time of the trial and, even today, the evidence that stenting improves clinical outcomes over and above those which can be achieved by balloon angioplasty alone remains limited, especially in patients with SLI/CLI as opposed to intermittent claudication.[139]

The high failure rate and reintervention rate reported after balloon angioplasty in BASIL have also been criticised. However, our data are similar to those presented by others in this group of patients with extensive multilevel disease.[140] Endovascular surgery is a rapidly developing field and new pharmacological[141,142] and procedural/device developments are likely to improve the results of endovascular therapies for lower limb ischaemia of all severities in the future.[140,143–148]

Choice of trial end points

The primary aim of the BASIL trial was to determine whether a bypass-surgery-first or a balloon-angioplasty-first revascularisation strategy was associated with a 'better' clinical outcome for patients. However, defining 'better' is not always straightforward and end point choices made by investigators clearly affect trial design, analysis and interpretation in a number of important respects. After much discussion, for the purposes of BASIL, we chose to define 'better' as improved AFS and used this as the primary end point for the power calculation and the prespecified statistical plan when finalising the design of the trial in 1998. We did so mainly because we believe AFS is the most clearly understandable and unambiguous measure of the primary purpose of revascularisation for SLI; namely to preserve limb and, so, life. Indeed, AFS remains the end point required by the US Food and Drug Administration for such studies.

Over the last 10 years our understanding of how the choice of single and composite clinical, and increasingly, surrogate end points can influence trial outcomes, interpretation, and so design, has become increasingly sophisticated. Used thoughtfully and transparently such end points can undoubtedly increase knowledge and understanding;[149] however, they can lead to a lack of clarity, an inability to compare different studies[150] and even to concerns around the appropriateness of regulatory approval.[151–153]

Some have queried why the BASIL trial did not use 'patency' as the primary outcome. However, we wished to compare two strategies, not just two 'one-off' procedures, and we wished to remain focused on important clinical outcomes. As such, we thought powering or interpreting the trial in the context of measures of haemodynamic success

(patency, ankle pressure), or other end points surrogating for meaningful clinical outcomes, would have been unsatisfactory.[154] Pragmatically, it is well recognised that assessing patency after balloon angioplasty in a uniform manner across 27 centres would have been logistically very difficult. Indeed, this is an issue that had bedevilled even very generously funded commercial studies of peripheral arterial endovascular interventions.[139]

Choice of entry criteria

It has been suggested that because the BASIL trial represents the 'tip of the iceberg' of patients with limb-threatening chronic ischaemia the data cannot be usefully generalised to everyday practice. As very clearly stated throughout the report, even in the very title of the trial itself, this was emphatically not a trial of patients with 'CLI' as defined by the European Consensus Document – the competent document in the UK at the time the trial protocol was finalised in 1998.

Rather, the patients admitted to BASIL had 'severe limb ischaemia' (SLI) which is the same as the European Consensus Document definition of CLI but, crucially, without the requirement to have an ankle pressure < 50 mmHg. This is perhaps a subtle but, nevertheless, a very important distinction that needs to be fully grasped to understand the aims, rationale and potential value of the BASIL trial in the context of everyday practice and the rest of the literature.

After much consideration, trial investigators and participants decided to admit SLI, and not just CLI, patients to the BASIL trial for a number of reasons:

- The 50-mmHg threshold is arguably an arbitrary cut-off. Does a patient requiring opiate analgesia for rest pain and with a gangrenous toe not have limb-threatening ischaemia and not therefore require immediate/early revascularisation just because their ankle pressure is 60 mmHg?
- Measurement of ankle pressure and pressure indices is subject to considerable inter- and intra-observer variation and interpretation.[41,155] Does a patient have limb-threatening ischaemia requiring immediate/early revascularisation on a day when their ankle pressure is measured at 45 mmHg but not on another day when their ankle pressure is 55 mmHg?
- When compared with bypass surgery, balloon angioplasty might well have the most to offer to those at the 'better' end of the spectrum of patients who have developed rest pain and tissue loss. Many of these patients will require immediate/early revascularisation to relieve severe pain and/or heal tissue loss but will have an ankle pressure above 50 mmHg. Would excluding such patients on the basis of an arbitrary haemodynamic cut-off from a trial where one of the arms was angioplasty make any sense?
- It became clear from our Delphi consensus studies (Chapters 8 and 9) that it was the minority of patients with, if you like, true CLI that were deemed by vascular surgeons and interventionalists (at that time) to have a pattern of disease that they believed was equally suitable for bypass and angioplasty (grey area of clinical equipoise).

Furthermore, at the time the BASIL trial was designed, Wolfe and Wyatt from the UK had recently written an influential paper describing what they termed subcritical limb ischaemia (SCLI),[40] which was defined as rest pain and ankle pressure > 40 mmHg; they redefined CLI as tissue loss and/or ankle pressure < 40 mmHg. These authors recommended on the basis of an analysis of 20 publications containing over 6000 patients that future studies should stratify by SCLI/CLI as the two groups had very different patterns of disease, responses to treatment and outcomes. More recently, other respected authorities have also recognised a similar group of patients who occupy a poorly defined haemodynamic area between disabling claudication and true CLI.[156,157]

Impressed by these scientific and logistical arguments, we chose to use the term 'severe limb ischaemia' to cover SCLI and CLI and to admit all such patients to the trial. However, in line with the recommendations of Wolfe and Wyatt we chose to stratify the randomisation according to whether the patient had rest pain only or tissue loss also and by whether or not their ankle pressure was < 50 mmHg (we chose 50 mmHg rather than 40 mmHg to be consistent with the European Consensus Document).

In fact, 336/452 (74.3%) of the BASIL patients had tissue loss which was very similar to that reported in many other studies of intervention for SLI/CLI. Only 93 patients had rest pain without tissue loss and an ankle pressure > 50 mmHg and 137 had an

ankle pressure < 50 mmHg. As expected from the randomisation process, these proportions were the same in both trial arms.

So, while it is true that the BASIL trial probably describes a group of patients who had, overall, less severe anatomic/clinical disease than studies where the 50 mmHg is strictly adhered to (CLI-only studies), we think that:

- the admission criteria were clear
- the admission criteria were appropriate given the aims of the trial
- all the patients randomised were thought at the time of randomisation to require early/immediate revascularisation to relieve pain and/or heal tissues loss and were quite clearly not, as has been suggested, only claudicants (this is discussed further below)
- by reporting transparently and in great detail the clinical and anatomic (angiographic) characteristics of the randomised patients, physicians will be able to make an informed judgement about the extent to which their patients are similar to/different from those described here (this is discussed further below).

It has been suggested that the fact that not all patients went forward to immediate revascularisation following randomisation indicates that many of the patients did not, in fact, have true limb-threatening ischaemia. The number of patients not receiving timely intervention was, in reality, small. In some cases this was because the patient's condition deteriorated and they became unfit for intervention, especially for bypass surgery; not surprisingly, such patients fared badly. In other patients the ischaemic pain/tissue loss improved with best medical and nursing care such that immediate revascularisation was not required or refused by the patient. As reported by Wolfe and Wyatt, some of these patients did quite well in the longer term without intervention. Even some patients with 'true' CLI deemed unsuitable for revascularisation have been reported to have quite low rates of short-term (6- and 12-month) limb loss and death with best medical and nursing care.[157] We believe that the BASIL data reflect the clinical realities of looking after this group of patients and demonstrate the value of developing predictive tools (see Chapter 5) that can help physicians match the available treatments to individual patients' needs and circumstances.[158]

Patient selection and trial generalisability

At one and the same time the BASIL trial has been criticised by some for studying a group of 'highly selected' patients that does not reflect the generality of patients affected by CLI (this has been discussed above) and by others for allowing too heterogeneous a group of patients to be randomised (not selective enough). We were well aware that, in common with every other RCT, when designing the BASIL trial there was going to be a trade-off between purity of sampling and generalisability that could never be fully resolved to everyone's satisfaction.

The BASIL trial audit found that c. 50% of patients presenting to six major UK vascular units (which together contributed c. 60% of the BASIL patients) with SLI due to infrainguinal disease were not considered suitable for, or to require, or to agree to immediate/early revascularisation. Some have expressed surprise at this statistic and suggested that it may be something unique to the UK health service. However, perusal of the literature reveals that few if any contemporary studies explicitly present data that allow the 'community' revascularisation rate in other countries to be determined.[159] The BASIL trial has been almost uniquely transparent in the SLI/CLI field of investigation by attempting to place the randomised patients with the total population of consecutive patients presenting with SLI to the major participating centres. Until data to the contrary are reported we think the BASIL audit data are likely to reflect practice to be found in many other health-care economies especially where, unlike in the UK, access to care is dependent upon an ability to pay at the point of delivery.

With regard to selection, during the 6-month BASIL audit (see Chapter 2), of the 236 patients presenting with SLI due to infrainguinal disease and who were considered to require and to be fit for immediate/early revascularisation, 70 (29%) were regarded as suitable for randomisation into BASIL. Of these, 22 (31%) refused trial entry and 48 (69%) were randomised.

It has been suggested that this is a highly selected cohort and that the BASIL trial data therefore have little relevance to the overall treatment of CLI. We have discussed this above but so crucial is this

issue to a proper understanding of the purpose, rationale, scope and value of the BASIL trial that the arguments bear further elaboration.

The aim of pragmatic RCTs like BASIL is to collect a heterogeneous group of patients requiring treatment (in this case for SLI) from a heterogeneous group of surgeons/interventionalists working according to their preferred methods in a large number of centres but then, crucially, to apply the rigour of randomisation to the treatment received. It is the polar opposite of the single-surgeon, single-centre 'experiences' of treating a more homogeneous group of patients in a highly standardised manner. The huge benefit of the former over the latter is that it provides a wholly unbiased report of what can be realistically achieved in the aggregate across a health economy through the application of two different therapeutic strategies where there is a genuine 'grey area of clinical equipoise'. Unlike all the other (uncontrolled) studies in the field that try to compare the surgical and endovascular treatment of SLI/CLI, the differences observed in BASIL between the two arms can only be the result of differences resulting from a bypass surgery versus a balloon-angioplasty-first strategy and not the result of selection bias.

With regard to 'selection', the BASIL trial is no different from, for example, the landmark carotid and aortic aneurysm trials that now guide intervention in those areas of vascular and endovascular surgical practice. Specifically, the BASIL trial compared (for the first and only time in a randomised manner) a bypass-surgery-first strategy with an a balloon-angioplasty-first strategy in patients who required and were fit for immediate/early revascularisation for SLI due to infrainguinal disease and who, in the opinion of the responsible surgeon and interventionalist, could be equally well treated by either bypass surgery or angioplasty (the grey area of equipoise).

So, of course, to be eligible for admission to the trial the patient had to:

- have SLI due to infrainguinal disease
- require and be fit for immediate/early revascularisation by either means
- have a clinical and anatomic (angiographic) pattern of disease that led both the surgeon and the interventionalist to believe there was a genuine grey area of equipoise.

As discussed above, about 30% of SLI patients were thought to meet these criteria and be eligible for the trial. The other 70% were considered (rightly or wrongly, we cannot say) to be better treated by bypass surgery, by balloon angioplasty, with best medical and nursing care only, or by primary amputation. Such patients could not therefore be randomised by those physicians.

The only other 'selection' was that the patients had to be able/willing to give fully informed written consent. Given the nature of the patients and the two treatments on offer a remarkably high proportion (c. 70%) of eligible patients agreed to be randomised; this is a great credit to the vascular teams in the 27 centres.

If readers choose to interpret this as 'selection' in the pejorative sense of the term then so be it. However, in keeping with all other RCTs, we could only randomise patients who were suitable for both treatment strategies and in whom there was genuine doubt as to which strategy would best serve their interests. To do otherwise would, of course, have been highly inappropriate both scientifically and ethically. All RCTs, including BASIL, work on the basis of the 'grey area of clinical equipoise' (uncertainty principle) which will, of course, (we know this from our Delphi consensus studies) vary between individual surgeons and interventionalists working in different units. Such judgements also change over time and it would be interesting to repeat the Delphi consensus studies that preceded the BASIL trial in the light of the BASIL trial data.

Power of the trial

Some have suggested that the BASIL trial is 'underpowered'; the investigators respectfully disagree. 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 AFS 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. In fact, these overall estimates turned out not to be unreasonable and 452 patients were randomised; of whom only four have been lost to follow-up. The other important point to make is that the real power of a trial depends more on the numbers of end points than on the number of patients randomised; and BASIL patients provided no shortage of end points (amputations, deaths). Of course, if one chooses to

embark upon subgroup analyses then the power weakens; but we have been careful not to do this. We have also been careful not to overinterpret the longer-term follow-up data; hence the decision to extend follow-up after reporting (what turned out to be interim) results in the Lancet in 2005.[50]

Prosthetic grafts

The BASIL trial investigators have been criticised for allowing the admission of prosthetic bypasses and the trial participants for failing to be sufficiently aggressive in using non-saphenous venous conduit. However, a review of the literature reveals conflicting views on the role of prosthetic bypass for SLI/CLI. While it is generally accepted that the results of prosthetic bypass are worse than those constructed with vein, and that the difference in performance increases as the grafts become more distal, it is clear that prosthetic grafts are still being widely promoted, and one presumes therefore used, for patients with SLI/CLI.[159,160] Various design modifications such as heparin-bonding and distal prosthetic pre-cuffing[160–162] are claimed to be effective in increasing graft patency to acceptable levels, even for tibial bypasses.[163,164] Others take the view that vein should be used at all costs and that even a high-risk non-saphenous, spliced venous conduit is always preferable to a prosthetic reconstruction.[159,165]

With regard to the BASIL trial, after considerable discussion and debate among the investigators and the participants, it was decided to allow the randomisation of patients who might require prosthetic bypass because in the UK (we suspect the same was true in most other developed countries) at the time the trial was designed (1997/1998):

- femorodistal bypass using a prosthetic conduit, usually with a venous cuff or boot, was a common operation
- vein bypass using non-saphenous conduit (for example, arm vein) was a much less common operation
- preoperative vein mapping was not universally available or used and, as a result, many patients would probably have been randomised only to become a protocol violation when the surgeon elected to use prosthetic rather than poor-quality non-saphenous vein during the surgery.

For these reasons, it was felt strongly that a vein-bypass-only trial would be unable to recruit sufficient numbers. A three-way trial of balloon angioplasty versus vein versus prosthetic bypass was briefly mooted but quickly discounted for clinical, logistical and statistical reasons.

In the event, about one-quarter of the bypasses undertaken in the BASIL trial were constructed with prosthetic material. Although non-randomised, by-treatment-received analyses have to be interpreted with great caution because of the risk of bias it does appear that prosthetic bypass performed very much less well in terms of AFS and to a lesser extent OS than either vein bypass or (transluminal or subintimal) angioplasty. There was no significant association between the use of prosthetic material, as opposed to vein, for bypass and any of the predictive baseline clinical variables (see Chapter 4). So, this lack of durability does not appear to be obviously the result of the selection for prosthetic bypass of higher-risk patients within the group randomised to surgery; rather it appears to result solely from a lack (in the opinion of the responsible surgeon) of suitable vein. So, although the data are not randomised, we feel that they offer reasonably convincing evidence for the superiority of vein (predominantly saphenous) bypass and, importantly, also balloon angioplasty over prosthetic bypass in this patient group.

It has been suggested (mainly by surgeons) that the exclusion of prosthetic grafts would have greatly improved the results of bypass and so made the advantages of surgery over angioplasty in terms of AFS and OS even more convincing, especially in the longer term. This may well be true. However, the investigators suggest that such a policy would probably have led to accusations of 'cherry picking' and bias from the interventional community. Specifically, it seems likely that interventionalists would have 'retaliated' by insisting that certain high-risk angioplasty cases, or immediate technical failures, be removed from the analysis.

Instead, we have conducted a large pragmatic multicentre RCT where all angioplasty and all surgical outcomes have been analysed by intention to treat. By permitting prosthetic bypasses within the trial, and by also offering a 'by-treatment-received' analysis (see Chapter 5), we have also been able to draw (with appropriate caveats) some conclusions about the relative merits of vein versus prosthetic bypass when compared with angioplasty. However, we must be very careful not to overinterpret non-randomised data.

Issues arising from the 'by-treatment-received' analyses

As discussed above in the context of prosthetic versus vein bypass, by-treatment-received analyses of RCT data must be undertaken and interpreted with great caution and we have quite deliberately presented these in a separate chapter (Chapter 5) from the intention-to-treat analyses (Chapters 2 and 3). It is important to appreciate that the validity of the conclusions and recommendations that can be drawn from a preplanned intention-to-treat statistical analysis of the randomised data from BASIL is very much greater than that which can be drawn from a post-hoc, by-treatment-received analysis. With respect to the latter, bias and confounding are unavoidable as a result of having lost the protection randomisation offers against such error.

Nevertheless, such analyses have been widely requested by clinical colleagues and, if conducted and interpreted transparently and appropriately, we believe that they can provide useful additional insights into the relative merits of the treatments being compared, as well as suggest further areas for research.

Such analyses are difficult to undertake in a group of patients who often have complex clinical journeys and multiple comorbidities, and where reintervention and crossover intervention are common, especially in the period following soon after randomisation. The investigators have had to make some decisions and assumptions to present what is a very complex picture in a manner that is comprehensible and clinically useful, but at the same time does not oversimplify the situation and so lead to erroneous conclusions and (over) speculation. We recognise that there are many different ways in which these analyses could have been done and not everyone would have chosen to do it as we have done.

Although the great majority of the patients randomised in BASIL underwent an attempt at their allocated treatment fairly soon after randomisation, as was to be expected, some of those interventions were significantly delayed; some of the first procedures were immediate technical or early clinical failures; some patients received the opposite intervention first; and a small number of patients received no attempt at revascularisation at all.

It is important to re-emphasise that BASIL was not a simple direct comparison of bypass and angioplasty. Rather, it was a comparison of a bypass-surgery-first with a balloon-angioplasty-first revascularisation strategy. Some commentators on BASIL have found that a difficult distinction to understand and appreciate. However, it is a very important difference because by comparing strategies we were able to compare not only the procedure(s) received, which may or may not have been the allocated one, but also what happened before and after that treatment.

With regard to what happens before the index procedure, one advantage of choosing a balloon-angioplasty-first strategy may be that, in general, the patient is more likely to be revascularised, and revascularised more quickly. This may be because admitting the patient to the interventional suite for a 1-hour procedure and then back to the main ward is logistically much easier than admitting them to an operating theatre for a 2-, 3- or 4-hour procedure and then back to a critical-care bed. Alternatively, it may be that patients going forward for balloon angioplasty are perceived to need less 'work-up' than those destined for bypass surgery.

With regard to events after the index procedure, we of course expected balloon angioplasty to be associated with a significant immediate technical and early clinical failure rate in this patient group; and we anticipated that a proportion of those patients would require further, often surgical, procedures. With respect to surgery, it was reasonable to expect the early failure rate to be lower but that reinterventions, either angioplasty or further open surgery, might be deemed necessary to maintain longer-term graft patency.

By comparing strategies we have been able to compare not just individual index procedures but also a wide range of other factors, some clinically driven and some logistical, that in reality impact the complex journeys these patients navigate before and after attempted revascularisation. Observational studies of particular groups of patients undergoing procedures are not sensitive to these sorts of important 'real-world' influences; in reality, they are difficult to perceive and quantify outwith the confines of an RCT.

As discussed above, patients randomised to bypass surgery first were less likely to undergo their assigned treatment. This group, the majority of whom had no treatment in the first 8 weeks following randomisation, differed little in terms

of baseline predictive factors (see Chapter 4) from those who did undergo their allocated treatment during the first 8 weeks. These non-operated patients appear to consist largely of patients who became too ill to undergo (or died before) surgery and those who declined surgery (sometimes because their symptoms improved, and sometimes because they changed their mind about what treatment they would accept). Two patients were not operated on because the surgeon could not find a suitable vein for bypass before surgery.

Any reader who looks after this group of patients will recognise the real difficulties inherent in randomising them to bypass surgery or balloon angioplasty. It requires a great deal of time to be spent with the patient and the family and it is a great credit to the teams in each of the hospitals that around 70% of those invited to take part in the trial accepted the offer.

Patients with no intervention in the first 8 weeks had an initially poor survival. However, subsequently, these patients appeared to fare as well as those undergoing successful first interventions in the first 8 weeks. We have discussed that issue above; suffice to say that others have reported surprisingly good outcomes in certain patients with unreconstructable CLI given best medical and nursing care. We think this observation in BASIL reflects the clinical reality in some patients presenting with SLI.

Results of surgery after failed angioplasty

It is often said, although on the basis of little real evidence, that an unsuccessful balloon angioplasty does not jeopardise the chances of subsequent bypass surgery in patients with SLI/CLI.[166] In other words, apart from the cost, there is 'nothing to lose' by at least trying balloon angioplasty first; if it works, then all well and good and, if not, then proceed to bypass surgery if required.[167] Notwithstanding all the caveats surrounding by-treatment-received analyses, the BASIL trial data do not appear to support this 'free shot' view of balloon angioplasty.

Patients with immediate or early balloon angioplasty failure did significantly worse in terms of AFS despite the fact that most went on to have apparently, at least initially, successful bypass surgery. This may be because failed balloon angioplasty simply identifies a group of patients who are going to do badly regardless of what surgical or endovascular treatment is offered. Alternatively, it may be that a failed angioplasty in some way jeopardises the chances of subsequent successful bypass in the longer term because it affects the type and extent of bypass required and/or the run-off. By looking at the perceived causes of angioplasty failure, comparing the characteristics of surgery undertaken as first procedure with surgery undertaken after failed angioplasty, and by looking at the causes of graft failure in those two groups, we hope to be able to gain some further insight into mechanisms behind the present observation; this work is ongoing and will be the subject of a future report.

However, for now, we can say with some confidence that about one-quarter of angioplasties performed for SLI are likely to fail immediately or within a few weeks and that, for reasons that are as yet unclear, such patients will tend to do badly even if they subsequently undergo, apparently initially successful, bypass surgery.

Issues arising from the prediction model

According to BASIL, being alive at 2 years after intervention appears to be the key factor that determines whether SLI patients are best served by a bypass-surgery-first or a balloon-angioplasty-first revascularisation strategy, Having been presented with these results, the BASIL trial participants, as well as surgeons and interventionalists from many other countries, strongly urged the trial investigators to try to construct a survival model that could help them judge which of their SLI patients are likely to survive for 2 or more years. In so doing, we were well aware of the methodological and interpretational challenges inherent in this work and that the estimates of survival produced must be used with great caution and in the context of the overall clinical situation for the individual patient.

Many different groups of researchers have attempted to create models and scoring systems that will accurately predict individual patient outcomes following various vascular and endovascular interventions. It is argued that used across different health economies such tools may:

- allow important clinical decisions to be made in a more scientific manner

- improve the process of obtaining informed consent from patients
- mitigate against medicolegal activity
- allow the performance of different clinicians and hospitals (even whole health-care economies) to be fairly compared in the context of differing case-mix
- improve cost-effectiveness and value for money, so protecting patients, providers and (where appropriate) the tax payer.

However, efforts to create such tools are fraught with methodological difficulties and many surgeons and interventionalists choose not to use them; preferring instead to rely on experience and intuition when making important clinical decisions about whether and how to treat their patients, including those with SLI.

While not wanting to devalue clinical experience or the 'art' of medicine, the problem with such an approach is that the same patient may be offered a wide variety of different treatments depending which clinician and institution they attend (we see that clearly in the Delphi consensus studies in Chapters 8 and 9). This non-evidence-based variability in practice appears increasingly out of step with what patients and (public and private) health-care purchasers expect of a 'respectable body of medical opinion'. At least in the UK, routine submission of detailed 'score-able' prognostic patient data to the National Vascular Database for the purposes of comparative weighted outcomes analyses is increasingly viewed as a *sine qua non* of reasonable, defensible practice.[158]

As discussed above, while present data confirm that while all patients with SLI are 'high risk', in reality they represent a heterogeneous group with regard to the risks of death, limb loss, and other major cardiovascular events over different time horizons. As others have observed, this complicates clinical decision-making,[168] especially when trying to balance short-term risks with longer-term durability in individuals who could reasonably be treated by either bypass surgery or balloon angioplasty.[169] The same types of trade-offs of course pertain to other vascular conditions, such as aortic aneurysm and carotid artery disease.

Many other groups have used observational, non-randomised data to try to predict various outcomes following interventions for SLI; a small selection of the largest and most recent studies are briefly summarised here.

In a study of over 4000 patients undergoing vein and prosthetic lower limb bypass in over 100 Veterans Affairs (VA) hospitals in the USA, investigators were able to stratify the risks of major amputation and death during a median follow-up of 44 months. They concluded that risk indices derived from the preoperative workup may be of use to clinicians in assessing and communicating risks and prognosis; and that risk-adjustment of outcomes is critical for evaluating future therapies in such patients.[170]

Low cardiac ejection fraction was found to predict a significantly shortened 2-year survival after infrainguinal arterial reconstruction and a trend toward increased perioperative major adverse clinical events.[171]

In a large series of diabetic patients undergoing saphenous vein grafts for lower limb ischaemia, investigators reported that they could predict 100% mortality at a median of 4 years follow-up using just four factors.[172] Within the PREVENT III cohort of 1404 patients undergoing infrainguinal vein bypass surgery for CLI a parsimonious risk stratification model ('PIII risk score') reliably identified a category of CLI patients with a > 50% chance of death or major amputation at 1 year.[173]

Going forward, it is hoped that the application of these, and perhaps the BASIL risk scoring system, may result in poor-prognosis patients being spared the risk, morbidity and cost of such surgery; being offered angioplasty or conservative treatment instead.

How did we choose which baseline variables to examine? Why did we not use other variables such as functional status, socioeconomic status, cultural factors, medical therapy, race and ethnicity, which other workers have considered equally important?

There is an almost limitless set of data that one could try to collect on every SLI patient due to undergo revascularisation in an attempt to predict with perfect accuracy the likely outcomes for each possible treatment methodology. Clearly this is logistically and ethically impossible. Furthermore, from a scientific point of view, such a 'fishing' exercise is likely to demonstrate very nicely the law of diminishing returns as the data collected become increasingly confounded and its collection *per se* will perturb, perhaps adversely, the true baseline state of the patient. So some selection and discretion has to be exercised.[172]

What clinicians have told us is that they want a survival model based on robust (objective) baseline variables that are easily and widely available in day-to-day clinical practice at the point of clinical decision-making with respect to pursuing a bypass-surgery-first or angioplasty-first strategy for their patients. When the BASIL trial was designed in 1997/1998 we discussed at length (as all triallists do) what information should be collected at baseline and during follow-up. Collect too little and readers may consider that the trial patients are being inadequately reported leading to a lack of confidence that the trial outcomes are properly generalisable. But, collect too much, and the data quality and completeness will inevitably deteriorate and there will be accusations of 'fishing'.

Race and ethnicity

Commentators on BASIL from other countries, notably North America, have stressed the importance of race and ethnicity on SLI/CLI outcomes. However, the problem with considering racial, social, economic and cultural factors in any prediction model is that they are very difficult to define for the purposes of scientific reporting; and may not travel well across national borders. Race,[174] socioeconomic class and educational attainment[172] are perhaps relatively less important in the UK where the population affected by peripheral arterial disease (SLI) is still largely white and where all citizens have equal access to health care and education free at the point of delivery funded through general taxation.[175] The question is whether this limits the usefulness of the BASIL trial in much of the rest of the world where this may not be the case?

Studies aimed at examining the links between race, ethnicity, the epidemiology and health outcomes from peripheral arterial disease, including SLI, are bedevilled with methodological problems and perhaps not surprisingly therefore the resulting data are inconsistent and conflicting.[175–177]

Some reports have found no effect for race after adjusting for social class and educational attainment.[175,178] Others have found ethnicity to be a strong and independent risk factor for peripheral arterial disease, which is not explained by higher levels of diabetes, hypertension and body mass index.[179] It has been suggested that African American status has a negative impact on the long-term outcome of infrapopliteal revascularisation, regardless of disease stage or associated risk factors.[180] Further, it has been hypothesised that such patients are biologically different in a way, as yet unknown, that may adversely affect the results of lower limb vein bypass.[174] Whether for socioeconomic or biological reasons, or both, data from the USA do appear to show a striking continuing difference in health-care outcomes for white and African American citizens affected by peripheral arterial disease[181–183] and many other diseases. Great care must therefore be taken when considering outcomes reported in observational case series and controlled trials, such as BASIL, whose cohorts may not reflect the nature of the unmet need in any particular country; especially where there is no universal health-care coverage.

In summary, a critical analysis of the literature shows that the data on racial, social, economic and cultural factors in this group of patients are extremely limited methodologically and that the conclusions, even apparently from within a single country such as the USA, are conflicting and largely unexplained to everyone's satisfaction. Lastly, it is clear that much of the predictive power of 'socioeconomic factors' on cardiovascular diseases operates through other factors like smoking and pre-existing disease, which are already in our model.

Best medical therapy

Given the available data (discussed above) showing the benefits of 'best medical therapy' on survival outcomes in patients with cardiovascular disease why not include, for example, statin use in our predictive model?

As discussed above, it is certainly the case that we have previously reported disappointingly low levels of 'best medical therapy' being implemented in patients at the time of randomisation into the BASIL trial. One would like to think that this simply reflects the study recruitment period and represents an historical problem now largely resolved. However, regrettably, similar levels of undertreatment in patients with peripheral arterial disease have been reported in recent large prospective studies conducted within centres of excellence within wealthy countries with very well-funded health-care systems.

The question is whether one should include different levels of best medical therapy in the prediction model. While it seems clear that statin use, for example, is associated with decreased cardiovascular mortality and amputation risk in SLI patients, we took the view that because

there is overwhelming level 1 evidence that every SLI patient should be considered for, and the great majority are taking, antiplatelet agents and lipid-lowering therapy (regardless of baseline cholesterol) we should not include these in our model. However, we are aware that others may take a different view and that, in the future, newer classes of drugs may also be shown to improve overall outcomes from lower limb revascularisation.

The BASIL survival prediction model

In summary, using only a small number of readily available unambiguous, and clearly definable, baseline clinical and anatomic (angiographic) variables (as opposed to a large number of variables, many of which are highly subjective), we have been able to stratify risk of death over 1 and 2 years within the BASIL cohort. Importantly, this represents the only modelling derived from data collected within the confines of an RCT comparing surgery and angioplasty. The factors included in the model were extremely strong predictors of outcome. Although it is possible that the other factors discussed above might be influential we think it unlikely that they would add much to what is already a highly predictive model. Scoring systems populated with variables that are reproducible across time and geography are perhaps more likely to be useful and used beyond narrow parochial boundaries.

The factors that were the most important predictors of survival are described in the following sections.

Age, history of myocardial infarction or stroke and tissue loss

It is widely reported that older patients, especially those over 80 years, are more likely to suffer complications and poorer outcomes following endovascular[184] and surgical interventions for lower limb ischaemia. The fact that significant cardiovascular and cerebrovascular disease portends a poor survival is not unexpected.

Ankle pressure and number of detectable ankle pressures

Although epidemiological data suggest that an abnormally high ankle pressure and pressure index (> 1.4) may predict an adverse cardiovascular outcome, we did not find this in the BASIL trial cohort. This may be because the observation is not transferable from population screening studies (where it presumably reflects vessel incompressibility and is essentially a surrogate marker for diabetes, which was of course included in our model) to patients with SLI, very few of whom are likely to exhibit such high pressures. It is generally accepted that low ankle pressures and indices predict poor cardiovascular outcomes. We also found this in the BASIL cohort. However, we found that number of detectable ankle pressures was more predictive than the highest ankle pressure (the pressure usually used to calculate ankle pressure indices). This is a novel finding that needs to be validated in other studies.

Serum creatinine

It is widely recognised and reported that even moderate impairment of renal function, as quantified for example by serum creatinine[185] or estimated glomerular filtration rate,[186] independently predicts increased mortality in vascular patients whether or not they are on dialysis.[182,187–189]

Smoking

It is no surprise that continued smoking portends a poor outcome in this group of patients although smoking histories are notoriously unreliable and we did not supplement self-reported smoking status with objective testing.[190]

Body mass index

We have found excessive mortality in underweight individuals. This observation, termed the 'obesity paradox', has been reported before in vascular patients and is thought to be at least partially explained by an over-representation of individuals with moderate-to-severe chronic obstructive pulmonary disease[191] and perhaps other types of chronic illness. Others have found that, despite a higher rate of perioperative technical difficulties and morbidity (especially wound infections), obese patients undergoing lower extremity arterial revascularisations have similar long-term patency, limb salvage and survival rates to those in non-obese patients.

Below-knee Bollinger angiogram score

It is widely recognised that increasing severity of lower limb disease, as measured by ankle pressures and the ankle brachial pressure index, is associated with increasing mortality whether or not the patients have symptomatic lower limb disease. Anatomic and haemodynamic burden of disease also affects outcomes after surgical and endovascular[192] lower-limb interventions.

Diabetes

It is widely reported that diabetic patients fare less well in terms of AFS and all-cause mortality following surgical and endovascular interventions for lower limb ischaemia.[172,182,193,194] This may be because diabetic patients present with more advanced and distal (tibial) disease that reduces run-off.

How might the BASIL prediction model be used by clinicians?

By exploring the influence on survival of a range of baseline factors, all easily obtained in routine clinical practice, we have tried to meet a clinical demand for a clinically useful tool based on the BASIL data. Notwithstanding the important issues around generalisability, and the methodological and interpretational difficulties inherent in the types of analyses discussed above, the specific intention here is to give clinicians an idea of how long an individual SLI patient (similar to those randomised in BASIL) might live. The clinician can, if they so choose, then use that information along with other data to counsel their patient, reach a decision about what treatment might be best, and take informed consent.

If the model suggests that there is only a 10% chance of the patient being alive at 2 years then the BASIL data suggest that a surgery-first strategy is unjustified. Rather, the appropriate choice would seem to be angioplasty or perhaps primary amputation or symptomatic medical treatment only. However, if the chances of the patients being alive at 2 years are predicted as 90% then the BASIL trial data suggest that a surgery-first strategy is best as the patient will probably survive to enjoy the longer-term benefits of surgery in terms of AFS and OS.

If the model predicts a 50/50 chance of the patient being alive in 2 years then that is helpful also. In this case the decision whether to attempt surgery or angioplasty first can reasonably be decided from other factors; for example, relative availability of institutional expertise with the two techniques, cost and, importantly, patient choice (based upon a full discussion of the likely medical journey the patient will take following each of the two strategies as described in this report).

In reality, many important clinical decisions are made on the basis of experience, hunch, intuition and patient choice (which may or may not be well informed and/or rational). There is often little alternative with regard to SLI/CLI because of the lack of good-quality comparative data to guide physicians and their patients. Notwithstanding the considerable difficulties of so doing, the aim of the BASIL trial was to apply some scientific rigour to the choice of surgery or angioplasty as first-line therapy where both seem possible and reasonable (as is the case in about a third of affected patients). The BASIL data suggest that the chances of being alive at 2 years after intervention is the key factor driving this decision and hence we have tried to model that using this survival prediction tool. Lastly, and perhaps most controversially, this prediction methodology could be used to define the characteristics of a group of patients whose outcomes are so poor, regardless of what method is used to try to revascularise their leg, that they would probably be better served by amputation or medical (symptomatic) treatment only. This potentially leaves the way open for an RCT of revascularisation versus primary amputation.

HRQoL, resource utilisation and cost-effectiveness

It is perhaps not surprising that in the short term (up to 12 months) surgery was about one-third more expensive than angioplasty. However, over the follow-up period as a whole, there was less of a difference between the two trial arms than might perhaps have been anticipated. This may reflect the fact that there is a wide range of (medical and social) factors, other than the status of the trial leg and its treatment, that determine admission, readmission and length of stay in hospital; and, despite the higher procedure costs and morbidity associated with surgery, patients randomised to angioplasty have a significantly higher immediate failure and reintervention rate.

Hospital costs were largely driven by the time spent in wards rather than in specialist HDU or ITU environments, or by procedures. Attempts to reduce costs could therefore be aimed at discharging patients from expensive acute wards to 'step-down' facilities for convalescence and rehabilitation where possible and appropriate. There was no attempt in the BASIL trial to collect medical or social care resource utilisation or cost data from outside hospital. However, it is reasonable to assume that such costs will be considerable (perhaps as much as the hospital costs) and broadly similar in the two trial arms.

A 3-year perspective suggests that surgery will be highly cost-ineffective when compared with angioplasty in terms of QALYs; an extra 10 days at a cost £3533 gives a 'cost per QALY' of £125,499. However, it is possible that in the longer term survival gains for surgery might translate into more impressive differences in quality-adjusted survival in favour of surgery. Hence, a 7-year (non-quality adjusted) perspective suggests the additional cost per AFS year is £20,579; and per year of OS is £29,095. However, there remains a substantial possibility that surgery may in fact remain cost-ineffective at broadly accepted WTP thresholds.

However, we also have to remember that the alternative to angioplasty or surgery for the bulk of these patients is death (an inexpensive option) or amputation – which we know is also an expensive option; although, as noted above, much of that cost would not necessarily be captured solely by estimating inpatient hospital costs. Indeed, in a purely hospital-cost analysis, even allowing for the cost of rehabilitation and limb-fitting, amputation may appear a cheaper option than either angioplasty or surgery because readmission is unlikely once they are discharged and many go on to die within a short period of time.

Can and should every patient be offered revascularisation?

Much of the available literature gives the impression that every patient who presents with SLI/CLI can and should be revascularised and that the results of those interventions are largely satisfactory. This is clearly not the case in the real world. In reality, many patients are not suitable or willing to undergo such interventions and in many cases the outcomes are extremely poor despite the expenditure of considerable resources. However, a significant proportion of such patients, even those with the most severe 'unreconstructable' disease, can be managed quite successfully, at least in the short term, with best medical and nursing care.[195,196] Many SLI/CLI patients with a very limited life expectancy and HRQoL are not well served by, often repeated, attempts at limb salvage.[197–201] While AFS is an appropriate and unambiguous primary trial end point, it does not give much information about the 'quality' of revascularisation. It is quite possible for a patient to enjoy a reasonable HRQoL with a primary amputation, especially if their premorbid mobility status was already limited, and for another patient to have a poor quality of life becase of chronic pain and wound problems despite an apparently 'successful' revascularisation.[154,198–202] The often assumed inverse relationship between revascularisation and amputation rates has not been borne out in an analysis of recent UK data.[203] It is very important, therefore, that vascular surgeons and interventionalists do not become excessively lesion-centric and undertake increasingly heroic attempts at limb salvage while losing focus on the individual patient's needs and expectations.[109,154,156,198–204] To try to assess these issues we have collected data on HRQoL, preintervention and postintervention ankle pressure, pain, ulcer healing, and the incidence and outcome of minor amputations. These data are being analysed and will be the subject of separate reports. Going forward, with the permission of the HTA, the BASIL investigators have also joined with their US colleagues under the auspices of the Society for Vascular Surgery to establish a working group to examine the data that might support objective performance goals for current and future CLI therapies. In so doing, the group recognises that large sample sizes are required to examine safety and efficacy, especially within critical subgroups. Data contributed from BASIL and other prospective multicentre studies are currently being used towards these ends.

Issues arising from the angiogram scoring study

Reasons for scoring the trial angiograms

When designing the BASIL trial the investigators and participants believed that for a number of reasons it was important to be able to describe the anatomic, or at least angiographic (lumenographic),[205] severity and extent of disease in randomised patients. First, we wished to be able to establish that patients in the two arms were anatomically (angiographically) comparable. Second, given the unique nature of the trial, we felt it was especially important to facilitate generalisation of the trial data to other groups of patients affected by similar anatomic (angiographic) patterns of disease; and, as an important corollary, not to those patients with different types of disease both clinically and anatomically. Third, we wished to explore the extent to which anatomic (angiographic) patterns of disease might predict outcomes (AFS, OS) for the BASIL cohort as a whole; and, fourth, whether it might be possible to predict likely success/failure

of bypass surgery and balloon angioplasty on the basis of the angiographic severity of disease.

To these ends, the 27 participating centres were asked to forward copies of preintervention imaging (in the great majority of cases this was intra-arterial digital subtraction angiography) for independent, blinded, batched analysis at the trial centre. In this paper we address aims one and two, as set out above, by presenting an analysis of those angiograms using the Bollinger scoring method and the TASC II classification. The relationship between the pattern and severity of disease and OS (aim three) has been reported in Chapter 4. Aim four is the subject of ongoing further analysis using different methodologies and tools.[205–216]

The angiographic characteristics of the BASIL trial patients

When considering the reporting of the BASIL trial it is very important to remember that BASIL is emphatically not a trial of all patients with SLI (of which patients with CLI are a subgroup) any more than other vascular RCTs have been a study of all aneurysms or all carotid artery disease or all claudicants, for example. Rather, BASIL was a trial of those SLI patients whose disease was due to infrainguinal disease; who were considered to require immediate/early revascularisation; and in whom the responsible surgeons and interventionalists felt there was a 'grey area of equipoise' as to the best manner in which to achieve that revascularisation. Specifically, patients were only eligible for randomisation in BASIL if there was true uncertainty as to whether a bypass-surgery-first or balloon-angioplasty-first revascularisation strategy was in the patient's best interests. As previously reported, this comprised about a third of the patients presenting to participating hospitals with SLI due to infrainguinal disease and about 70% of those eligible patients were randomised.[2]

The Delphi consensus studies that preceded the trial suggested that at the commencement of the trial many UK vascular units were offering angioplasty in preference to bypass to SLI patients at the 'good' end of the anatomic/clinical disease spectrum. By contrast, those with the severest disease were largely being offered femorodistal bypass surgery rather than angioplasty. So, in a trial that compared a bypass-first with an angioplasty-first revascularisation strategy in patients thought to be suitable for both it was highly likely that the type of bypass surgery undertaken was going to be less 'distal' overall than the totality of surgery undertaken for SLI/CLI. Similarly, the extent and complexity of the balloon angioplasty undertaken in BASIL was likely to be significantly greater than commonly reported in patients being treated for disabling claudication. The present data lend general support to these presumptions although further work is under way to determine if the nature of the bypasses and angioplasties undertaken in BASIL changed during the recruitment period. Analysis of the Bollinger scores shows that the two trial arms were very well matched and that BASIL patients with the least overall burden of disease tend to have that disease concentrated in the SFA and popliteal artery. However, as the overall severity of disease increases, the below-knee arteries become increasingly diseased; the posterior tibial was the worst affected crural artery while the peroneal appears relatively spared. Interestingly, but perhaps not surprisingly given the above considerations, there was a highly significant negative correlation between mean above-knee and the mean below-knee Bollinger scores. As a consequence, most BASIL patients had severe disease below the knee. As suggested above, it appears likely that patients with mild to moderate disease above and below the knee were not considered eligible for randomisation in BASIL either because their disease was not severe enough to cause SLI or because they were considered best treated by angioplasty (no clinical equipoise). Similarly, it appears that patients with severe disease above and below the knee were not eligible for randomisation because they tended to be considered by the responsible vascular teams as best treated by bypass (again, no clinical equipoise). It is clearly very important that these considerations and the patterns of disease described here are kept in mind when interpreting the results of the BASIL trial, especially when trying to extrapolate the recommendations to other groups of SLI patients.

The angiographic data presented here are reflected in the bypass and angioplasty procedures undertaken in BASIL. Most bypasses originated at the common femoral artery although around a fifth commenced at the level of the knee. The site of the distal anastomosis was divided approximately equally between the above-knee popliteal, below-knee popliteal and crural arteries. Of the infrapopliteal bypasses, 25% were to the posterior tibial; 36% to the anterior tibial; 32% to the peroneal artery; 25% were proximal third; 29% were middle third; 40% were distal third; there were a small number of grafts to the tibial

peroneal trunk and three grafts to the dorsalis pedis artery. About one-quarter of the grafts involved the use of prosthetic material either wholly or as part of a composite graft; these were fashioned with or without a vein cuff in approximately equal numbers. Over 90% of vein bypasses were constructed predominantly with the ipsilateral great saphenous vein. With regard to the angioplasty, in about three-quarters of patients interventionalists reported that they had attempted to treat a single length of disease (which often spanned several anatomic segments); in the remainder attempts had been made to treat more than one (up to four) separate disease lengths. The numbers of reported transluminal and subintimal angioplasty were approximately equal with just over 10% being reported as mixed. The majority of patients (80%) underwent treatment of the SFA either alone (38%) or in combination with the popliteal artery (42%) and crural arteries (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 angioplasty was small. Reviewers have criticised the lack of foot views of sufficient quality to allow reliable scoring of the plantar arch. We agree that best current practice involves the generation of such images and that the inclusion of plantar arch data in various 'run-off' scores may add predictive value (although this was not the subject of the present report). However, in the population of patients eligible for randomisation in BASIL where suitability for angioplasty was a sine qua non, for the reasons suggested above, plantar arch data may not have been as informative as in the whole SLI/CLI population.

Choice of scoring systems

Various angiographic and 'run-off' scoring systems have been described; each has different characteristics, strengths, weaknesses and purposes. As discussed above, the purpose of the present study was to describe the angiographic patterns of disease in the BASIL cohort as a whole and in the two arms separately. The purpose was not to try to relate procedural (bypass or angioplasty) outcomes to the anatomic severity and extent of disease or, specifically 'run-off'; those analyses are ongoing and will be the subject of a separate report. It was agreed at the outset of the trial that we would use the Bollinger scoring system to describe the extent and severity of disease in the BASIL patients as it appeared to be reasonably 'user-friendly' while at the same time offering considerable detail throughout the infrainguinal arterial tree. When the trial protocol was agreed, the TASC classification system did not exist.[1] Furthermore, given that the TASC system largely restricts itself to the femoropopliteal system, and that most BASIL patients were likely to also have significant infrapopliteal disease, we had not intended to use the TASC system. However, many surgeons and interventionalists asked us to also describe the BASIL patients in terms of TASC II group, which we have done. There was never any intention to formally test Bollinger against TASC II; indeed, given that the two systems are so different in method, scope and purpose we think it would be inappropriate to do so. Not surprisingly then, although the TASC II and Bollinger scores were generally related, for the reasons give above, there were also cases where they disagreed. This is because the TASC II classification, by not incorporating an assessment of infrapopliteal disease, gives a less complete assessment of the type of patient entered into the BASIL trial. Discriminating between SLI patients with different extents and severities of infrapopliteal artery disease appears likely to be important in predicting the success of, and so the suitability for, different treatments as well as overall outcome.[6]

Conclusions

Anatomic (angiographic) disease description in patients with SLI requires a scoring system that is sensitive to differences in femoropopliteal and infrapopliteal artery disease. The Bollinger system appears well suited for this purpose, is easy to use and is associated with low levels of intra- and interobserver error. The utility of the TASC II classification in SLI/CLI patients appears limited by its lack of anatomic scope. The present analysis confirms that, as expected from the randomisation process, the patients in two arms of the BASIL trial were well matched in terms of anatomic (angiographic) patterns of disease. The detailed angiographic analysis presented here will facilitate appropriate generalisation of the trial data to other groups of patients affected by similar anatomic (angiographic) patterns of disease.

Final thoughts

In summary, therefore, the BASIL trial is the only RCT to have compared the surgical and endovascular management of patients with limb-threatening chronic ischaemia due to infrainguinal peripheral arterial disease. The BASIL trial

participants and investigators therefore hope that the results of this major HTA-funded, multicentre, randomised controlled UK trial will have a global impact on the management of SLI and be of interest to a large and diverse worldwide readership including:

- patients and the general public: because many are affected directly or indirectly by SLI, a condition about which there is a low level of public knowledge and awareness when compared with, say, 'heart attack' or 'stroke'
- epidemiologists: because it provides new information about the severity and natural history of the disease
- general practitioners and primary-care physicians: because it has important implications for the diagnosis and treatment of affected patients in the community, as well as for onward referral and 'shared-care' arrangements
- nurses and other allied health-care professionals: because in many countries it is they who, at least initially, often assess and manage affected patients in primary and secondary care
- vascular surgeons and interventional radiologists: because the data have important implications for the treatment of patients in secondary care and the training of vascular and endovascular surgeons
- health economists, the Department of Health and Primary-Care Trusts: because the data have important implications for health-care commissioning in terms of the most appropriate use of limited health-care resources
- industry: because numerous companies and commercial organisations are investing heavily in research and development relating to interventional devices and pharmacotherapy for the treatment of SLI
- research commissioning bodies: because these novel data will suggest where further research in this area is required
- developing countries: because SLI is a growing problem in developing countries and these data will be of value to all the stake-holders in such health economies as they plan appropriate services for affected patients.

Chapter 11

Summary, implications for practice and research recommendations

Summary

Trial objectives

The principal aim of the BASIL trial was to compare, for the first time in a multicentre RCT, the outcome of a 'bypass-surgery-first' with a 'balloon-angioplasty-first' strategy in terms of AFS (the primary end point), all-cause mortality (ACM; also known as OS), HRQoL, post-procedure morbidity and mortality, reinterventions and the cost-effective use of hospital resources.

Other objectives were:

- to examine baseline factors affecting the outcome of the trial cohort
- to describe the angiographic pattern and severity of disease in patients randomised within the trial
- to compare outcomes from different types of surgical bypass and angioplasty
- to use a Delphi consensus method to examine the level of agreement among vascular surgeons and interventional radiologists regarding their preference for the surgical or endovascular management of SLI and to examine the angiographic and clinical factors which might influence those preferences.

Power calculation

The sample number calculations proposed that 223 patients per treatment arm would be needed for a 90% power to detect a 15% difference in 3-year AFS at the 5% significance level.

Methods

- Between August 1999 and June 2004 452 patients were randomised (by centre, clinical presentation and ankle pressure) to bypass surgery (n = 228) or balloon angioplasty (n = 224) at one of 27 UK hospitals.
- Preintervention angiograms of the trial leg were scored using the Bollinger and TASC II methods.
- Data were collated centrally and confidentially at the trial office based in the University Department of Vascular Surgery, Heart of England NHS Foundation Trust, Birmingham, UK.
- During a 6-month period, 585 patients presenting with SLI to the six top-recruiting centres were audited to assess trial generalisability (the BASIL trial audit).
- We measured self-reported HRQoL using the EQ-5D, the SF-36 and VascuQoL at baseline and at 3, 6 and 12 months after randomisation.
- We obtained patient-specific resource use and costs on first and all subsequent interventions and hospital stays during follow-up.
- All patients provided written informed consent and the study was approved by the Multicentre Research Ethics Committee for Scotland. The BASIL trial was registered with the National Research Register and the International Standard Randomised Controlled Trials Number Scheme (ISRCTN45398889).
- Follow-up data were prospectively recorded by research nurses.
- Other information was obtained from the ISD of the NHS in Scotland using record linkage to Scottish Morbidity Records (SMR1) and General Registrar Office (Scotland) GRO(S) death records, paper hospital records, electronic hospital information systems and general practitioners.
- Before the trial commenced, a Delphi consensus study using 596 different hypothetical patient scenarios and a panel of 20 consultant vascular surgeons and 17 interventional radiologists was undertaken.

Results

Delphi consensus studies

- A Delphi consensus study revealed substantial levels of disagreement (81% of scenarios in round 1 and 67% in round 2) between and among surgeons and radiologists with regard to the appropriateness of surgery or angioplasty for SLI over a wide range of clinical and angiographic severities of disease.

- This disagreement was greater among surgeons than radiologists in both round 1 (83% vs 65%) and round 2 (69% vs 42%).
- Surgeons also demonstrated less convergence between rounds.
- Further analysis reveals that this disagreement relates to the fact that surgeons and radiologists view the risks and benefits of their own, and their counterparts', treatment modality differently in the context of a similar angiographic pattern of disease and clinical.
- Increasing disease severity, the absence of run-off into the foot, the presence of a suitable vein and tissue loss as opposed to rest pain only (the latter only significant for surgeons) all increased the mean response score towards surgery.
- However, surgeons and radiologists weighted each of these factors quite differently.
- Even in the most complex statistical model, 19% of surgical and 13% of radiological response variation remained unexplained. This re-emphasises the need for joint surgical and radiological decision-making and the need for excellent communication so that colleagues are not working at cross-purposes or with misconceptions.

BASIL trial audit

In the BASIL trial audit approximately half of patients presenting to the top six trial recruiting centres with SLI underwent early/immediate revascularisation; of these, approximately 30% were potentially eligible for randomisation and, of these, 70% of these were randomised.

Clinical and angiographic severity of disease

- Trial patients were well matched in terms of baseline clinical data and angiographic severity and extent of disease.
- Preintervention angiograms were available and of sufficient quality to be scored for 418 of 452 (92.5%) randomised patients; 12 were TASC II type A (least severe), 122 were type B, 186 were type C and 93 were type D (most severe).
- Patients with the least overall disease tended to have their disease concentrated in the SFA and popliteal artery which were the commonest sites of disease overall.
- As the overall severity of disease increases, the crural arteries become increasingly involved in addition to the more proximal disease.
- The posterior tibial was the worst affected crural artery while the peroneal appeared relatively spared.
- There was general agreement between TASC II, BASIL randomisation group and Bollinger although the level of agreement is quite low and there are many patients where they are not in agreement.
- Over 40% of patients had diabetes, over a third were still smoking, three-quarters had tissue loss, over 50% had an ankle pressure < 50 mmHg; a quarter had bilateral SLI, and most were elderly with a significant cardiovascular past medical history.
- Despite this, one-third of patients were not receiving an antiplatelet agent and only one-third of patients were receiving a statin when referred for vascular surgery.

Procedures

- Approximately 25% of bypasses involved prosthetic material; two-thirds were to the popliteal artery and one-third to a crural artery.
- Approximately a third of angioplasties were transluminal; one-half were subintimal (the rest mixed); one-quarter involved only the SFA; one-half involved the popliteal artery; and one-quarter involved the crural arteries..

Interim intention-to-treat analysis – 2005

- Following randomisation, 195/228 (86%) patients randomised to bypass surgery and 216/224 (96%) to balloon angioplasty underwent an attempt at their allocated treatment at a median (interquartile range) of 6 days (3–16 days) and 6 days (2–20 days) respectively.
- An intention-to-treat analysis shows that a bypass-surgery-first strategy was associated with significantly lower immediate failure (3% vs 20%), higher 30-day morbidity (57% vs 41%) and lower 12-month reintervention (18% vs 26%) rates than a balloon-angioplasty-first strategy.
- The 30-day mortality was similar (surgery 5%, angioplasty 3%).
- By February 2005, 99% of patients had been followed up for 1 year, 74% for 2 years, 48% for 3 years, 22% for 4 years and 8% for 5 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 having their trial leg amputated and 130 (29%) had died with their trial leg intact.
- Survival to the primary end point at 1 and 3 years was not significantly different between the two trial arms; 68% and 57% for those randomised to a bypass-surgery-first strategy

and 71% and 52% for those randomised to a balloon-angioplasty-first strategy.
- A post-hoc analysis, carried out following examination of the survival curves, found a significantly reduced hazard in terms of AFS (adjusted HR 0.37; 95% CI 0.17 to 0.77; p = 0.008) and ACM (adjusted HR 0.34; 95% CI 0.17 to 0.71; p = 0.004) for bypass surgery relative to balloon angioplasty in the period beyond 2 years from randomisation.
- There were no significant differences in HRQoL between the two groups. Over the first 12 months, patients randomised to bypass surgery spent significantly longer in hospital and required significantly more HDU (23% vs 7%) and ITU (4% vs 0.5%) care than those randomised to balloon angioplasty.
- As a result surgery was approximately one-third more expensive over the first 12 months.
- As a result of these data, an additional grant application to the HTA to follow the patients for a further 2½ years was successful and all patients have now been followed for 3 years and more than half for over 5 years.

Final intention-to-treat analysis – 2008
- A final intention-to-treat analysis (based on the prespecified statistical plan) of clinical effectiveness and cost-effectiveness, as well as several substudies, has been undertaken during 2008.
- Apart from four patients lost to follow-up, there is now a minimum of 3 years complete follow-up for all patients with 54% of patients being followed for more than 5 years; the longest follow-up was just over 7 years. At the end of final follow-up, 250 (56%) patients were dead. Thirty (7%) were alive with amputation of the trial leg, and 168 (38%) were alive with no amputation (four patients lost to follow-up).
- A Cox proportional hazards model has identified the following baseline factors to be independent predictors (in descending order of importance) of AFS and death from any cause for the whole cohort over the whole follow-up period: BASIL randomisation stratification group, below-knee Bollinger scores, body mass index, age, diabetes type I and type II together, creatinine, smoking.
- Patients who survived 2 years and who were initially randomised to surgery gain a significant c. 7 months of additional life (95% CI, 1 month to 13 months)and an additional non-significant c. 6 months of amputation-free life (95% CI 0 months to 12 months) over the subsequent follow-up when compared with those randomised to angioplasty.
- Over the first year from randomisation the mean cost of inpatient hospital treatment in patients randomised to surgery was estimated at £22,002 (£18,369 hospital stay and £3635 procedure costs), which is approximately a third higher than the £16,582 (£14,468 hospital stay and £2115 procedure costs) for patients randomised to angioplasty.
- This difference in mean total hospital and procedures costs of around £5420 was significant (95% CI £1646 to £9195) at 1 year.
- However, because of the increased costs incurred by the angioplasty patients in years 2 and 3, this difference decreased to £3533 (£29,006 surgery vs £25,472 angioplasty) and was no longer significant by the end of year 3.

Final 'by-treatment-received' analysis – 2008
- Patients receiving initially successful vein bypasses did better that those receiving initially successful prosthetic bypasses ($p < 0.01$ for AFS, $p = 0.11$ for OS, log-rank tests).
- There was no significant association between the use of prosthetic material for bypass and any of the baseline clinical data.
- There were no differences in terms of AFS and OS, respectively, between the different types of angioplasty.
- Prosthetic bypass also performed significantly worse than both transluminal and subintimal angioplasty.
- Patients randomised to angioplasty and who underwent bypass surgery after failed angioplasty did significantly worse in terms of OS, but especially AFS, than those who were randomised to and underwent bypass surgery as their first treatment.

Prediction model
- By exploring a wide range of baseline clinical and angiographic factors, all easily obtainable in routine clinical practice, it has proved possible to develop a prognostic model for survival up to 2 years from randomisation.
- The most important predictors were age, presence of tissue loss, smoking and a history of angina or myocardial infarction
- Other factors include serum creatinine, history of stroke or transient ischaemic attack, below-knee Bollinger score, body mass index, number of recordable ankle pressure measurements and the highest ankle pressure.

- Together, these factors can be used to reliably identify patients who are unlikely to live for more than 2 years after intervention and who, therefore, are unlikely to enjoy longer-term benefits of surgery.
- The model has been incorporated into an EXCEL spreadsheet that can be used to predict survival to 6 months, 1 year and 2 years for future patients.

HRQoL

- HRQoL response rates fell significantly over time (c. 70–75% at 12 months and c. 40% at both 24 and 36 months) but were very similar for all HRQoL instruments used (SF-36, VascuQoL and EQ-5D) and in the two arms.
- An analysis of recorded (non-imputed) data shows that HRQoL is non-significantly better in the surgery group both before and after randomisation.
- An analysis of imputed (for missing values) EQ-5D data shows that amputation is associated with a significant reduction in HRQoL and that surgery is associated with better HRQoL at all time intervals out to 3 years.

Resource utilisation: length of stay in hospital

- The use of inpatient hospital services over time was broadly similar in both trial arms as measured by the number of hospital admissions and total days spent in hospital.
- Over the first year from randomisation, patients in the surgery group were in hospital for about a week longer than those in the angioplasty group.
- The difference in hospital stay shifted in favour of surgery over the longer run as the angioplasty patients used slightly more inpatient care over the medium to long run.
- Over a 7-year time horizon the average number of hospital stays for both groups was four and the average length of stay, averaged over all inpatient admissions, was just over 2 months (71 days).
- On average, therefore, BASIL patients spent 5–6 weeks of their first post-randomisation year in hospital and then 2–3 weeks per year thereafter.
- Patients spent most of their time in hospital in the wards and there was relatively little use of the more specialised services provided in HDU and ITU.
- Patients randomised to a surgery-first strategy used around half a day more of HDU and a few more hours of ITU than those randomised to angioplasty. However, the main cost driver remains the duration of ward stays.

Resource utilisation: hospital costs

- Over the first year from randomisation the mean cost of inpatient hospital treatment in patients randomised to surgery was estimated as £22,002 (£18,369 hospital stay and £3635 procedure costs), which is approximately a third higher than the £16,582 (£14,468 hospital stay and £2115 procedure costs) for patients randomised to angioplasty.
- This difference in mean total hospital and procedures costs of around £5420 was significant (95% CI £1547 to £9294) at 1 year.
- However, because of increased costs incurred by the angioplasty patients in subsequent years, at the end of 7 years, this difference decreased to £2310 (£33,539 surgery vs £31,228 angioplasty) and was no longer significant.
- After 3 years of follow-up, procedure costs accounted for 9% of total hospital costs in the angioplasty-first group compared with 14% for the surgery-first group. Most of the procedure costs are incurred in the first year following randomisation.

Resource utilisation: cost-effectiveness

- If we first take a 7-year (non-quality-adjusted) perspective we find that patients randomised to surgery are estimated to live, on average, 41 days longer with their trial leg intact at an estimated additional average hospital cost of £2310 when compared with those randomised to angioplasty.
- The additional cost per AFS year is, therefore, £20,579 [£2310/(41/365.25)].
- Similarly, when the estimated additional hospital cost of surgery out to 7 years (£2310) is compared with the additional estimated average gain in OS (29 days) the point cost-effectiveness ratio is £29,095 [£2310/(29/365.25)].
- If we now take 36-month quality-adjusted perspective, we find the small positive differences in HRQoL (imputed EQ-5D) in favour of surgery, combined with the small (34 days) advantage for angioplasty in terms of absolute survival, generates a mean quality-adjusted life time of 442 days for angioplasty and 452 days for surgery [mean difference 10 days (95% CI, –48 to 68), not significant].
- This extra 10 days is obtained at an estimated additional average hospital cost of £3533 for surgery, giving a point estimate of the cost-effectiveness of surgery compared with

angioplasty over 3 years, the 'cost per QALY', of £125,499 [£3533/(10/365.25)].
- If we now look at the relationship between bootstrapped estimates (5000 resamples) of the differences in cost and the differences in amputation-free life-years out to 7 years we find that about half of the distribution indicates surgery to be more expensive but better in terms of AFS. However, the distribution also extends well into the more expensive, fewer amputation-free life-years sector.
- Incremental cost-effectiveness ratios at different levels of WTP can be used to create cost-effectiveness acceptability curves which show the probability that a surgery-first strategy is cost-effective, assuming different ceiling levels for the value placed on an amputation-free life-year.
- At a WTP value of £20,579 the probability is, by construction, equal to 0.5 as this is the point estimate of the cost-effectiveness ratio.
- The curve is relatively flat beyond this point suggesting that even when higher values are placed on an additional amputation-free life-year (e.g. > £50,000) the probability that surgery is cost-effective is only ever around 0.6 to 0.7.

Implications for practice and research recommendations

The greatest gains in SLI lie in early diagnosis, best medical therapy and prompt referral

Looking at the BASIL trial patient histories it is clear that in most cases their SLI developed slowly over months and often years. Despite this, and also being at exceptionally high risk of cardiovascular events, many patients:

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

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

- detecting lower limb arterial disease at an earlier stage (before it becomes life-threatening and limb-threatening)
- ensuring that all patients with peripheral arterial disease are offered 'best medical therapy'
- ensuring appropriate and prompt referral to a vascular unit for specialist care

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

Multidisciplinary team working

It seems clear from the BASIL trial data that the best outcomes for SLI are achieved when vascular surgeons and interventionalists work closely together with nursing and colleagues from other professions (physiotherapy, occupational therapy, rehabilitation services, orthotists and prosthetists) as part of a multidisciplinary team. It seems likely, therefore, that SLI is another example of where vascular care is best delivered in specialist, high-volume centres. This requires further evaluation but is entirely consistent with the general direction of travel regarding training in, and delivery of, vascular services in the UK (www.vascularsociety.org.uk/Docs/POSPVD%2008%20final%20draft.pdf).

Delphi consensus studies

The Delphi consensus studies performed before the BASIL trial commenced showed high levels of interprofessional and intraprofessional agreement among vascular surgeons and interventionalists. It would seem highly desirable to repeat these studies to determine whether there has been any convergence of views as to the relative merits of bypass surgery and balloon angioplasty in SLI patients in the light of the BASIL trial data.

Treatment recommendations based on BASIL trial results

The clinical outcome data from our study suggest that in SLI due to infrainguinal disease requiring immediate/early revascularisation, patients expected to live:

- less than 2 years should usually be offered balloon angioplasty first; especially where there is no vein for bypass
- more than 2 years should usually be offered bypass surgery first; especially where vein is available for bypass.

Validation of the BASIL trial prediction model

Given that the main factor determining whether a bypass-surgery-first or a balloon-angioplasty-first strategy is preferable in patients with SLI who could be treated by either method appears to be the likelihood of them being alive at 2 years, it would seem important to validate the BASIL trial survival prediction model in a separate cohort of 'BASIL-like' patients.

Role of prosthetic bypass in the management of SLI

Patient outcomes following prosthetic bypass in the BASIL trial were extremely poor. It seems clear that vascular surgeons should use vein for bypass surgery wherever possible and view prosthetic bypass as very much a last resort. Even in patients expected to live more than 2 years it appears likely that attempting balloon angioplasty in the first instance is preferable to embarking upon prosthetic bypass. In some cases even primary amputation would seem preferable.

Role of endovascular therapies in the management of SLI

In keeping with other studies the immediate technical and early clinical failure rate of balloon angioplasty in the BASIL trial was high (25–30%). There is clearly an urgent need for further research to:

- identify those patients and anatomies where angioplasty is unlikely to be successful
- understand the mechanisms of failure
- develop new procedures, techniques and devices (such as stents and stent-grafts) that will increase the success of peripheral vascular endovascular interventions both initially and in the longer term.

Summary of implications for practice

We suggest that the main implications for practice are the following:

- Public-health/primary-care/secondary-care measures aimed at:
  - detecting lower limb arterial disease at an earlier stage (before it becomes life- and limb-threatening)
  - ensuring that all patients with peripheral arterial disease are offered 'best medical therapy'
  - ensuring appropriate and prompt referral to a vascular unit for specialist care

should be priorities for health services.

- Patients with SLI due to infrainguinal disease requiring revascularisation and who are expected to live less than 2 years should usually be offered balloon angioplasty first; especially where there is no vein for bypass.
- Patients with SLI due to infrainguinal disease requiring revascularisation who are expected to live more than 2 years should usually be offered bypass surgery first; especially where vein is available for bypass.
- The use of prosthetic bypass for the treatment of SLI due to infrainguinal disease should be discouraged as such grafts are expensive and they perform poorly in this group of patients.
- Rehabilitation, limb-fitting and social services for vascular amputees require re-evaluation so that these amputees can enjoy the best quality of life possible and so that available resources can be used in the most clinically and cost-effective manner.
- Where possible, patients with SLI should be treated in specialist, high-volume centres where multidisciplinary teams can offer the full range of treatment and support services required in the most clinically effective 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 patients in the light of the BASIL trial data.
- To confirm or refute the BASIL findings and recommendations in further RCTs. (Given the health and socioeconomic burden imposed by SLI it seems extraordinary that BASIL remains the only RCT to compare the surgical and endovascular treatment of this condition. 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. The need for further publicly funded

trials in peripheral vascular disease would seem clear.)
- To validate the BASIL trial survival prediction model in a separate cohort of SLI patients.
- To compare the clinical effectiveness and cost-effectiveness of (endovascular) revascularisation versus primary amputation versus best medical and nursing care only in poor prognosis patients.
- To examine the clinical effectiveness and cost-effectiveness of new endovascular techniques and devices (such as stents and stent-grafts) in the management of SLI.

The care of vascular amputees

It is clear from the BASIL trial that, regrettably, many patients with SLI soon require major limb amputation despite the best efforts of vascular surgeons and interventionalists to try to save the limb. The BASIL resource utilisation data also show that amputees tend to spend long periods on acute surgical wards where they consume (at considerable expense) acute resources they do not need but where they cannot receive the rehabilitation they do need. There would seem to be an urgent need to rethink services for vascular amputees so that they may enjoy the best quality of life they can and so that resources can be used in the most clinically effective and cost-effective manner.

Optimising models of care for patients with SLI requires further evaluation – the role of amputation in the management of SLI

The BASIL trial clinical and resource utilisation data, taken together with the prediction model, suggest that the interests of a significant proportion of BASIL patients might have been best served by primary amputation, followed by high-quality rehabilitation, rather than often repeated, unsuccessful attempts at revascularisation. Although controversial, the BASIL trial leaves the way open for a trial of (probably largely endovascular) revascularisation versus primary amputation versus best medical and nursing care only in selected poor prognosis patients.

RCT of (probably largely endovascular) revascularisation versus primary amputation versus best medical and nursing care only in selected poor prognosis patients – the need for further publicly funded RCTs in peripheral vascular disease

Given the socioeconomic burden that SLI places upon developed and increasingly developing nations it seems quite extraordinary that, to our knowledge, BASIL remains the only RCT to compare the surgical and endovascular treatment of this condition. Further comparable trials are clearly required to confirm or refute the BASIL findings and recommendations. We strongly believe 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 primarily driven by commercial interests. The need for further publicly funded trials in peripheral vascular disease would seem clear.

Publicly funded RCTs in peripheral vascular disease

Further publicly funded RCTs in peripheral vascular disease are required.

Acknowledgements

BASIL trial participants and contributors

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Publications

Bradbury A, Bell J, Lee AJ, Prescott RJ, Gillespie I, Stansby G, et al. Bypass or angioplasty for severe limb ischaemia? A Delphi Consensus study. Eur J Vasc Endovasc Surg 2002;**25**:411–16.

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Appendix 1
BASIL trial protocol

Background

The incidence of SLI in Great Britain and Ireland is currently estimated at 40 per 100,000 per year. The cost of the condition is more than £1 billion per annum. The ageing population, the increasing prevalence of diabetes and the failure to reduce tobacco consumption mean that this incidence is likely to increase. Without revascularisation, the majority of patients with SLI will require major limb amputation. Amputation is associated with loss of independence, a significant reduction in quality of life (QoL) and high levels of direct and indirect NHS expenditure for rehabilitation, social support and long-term institutional care. It is clear, therefore, that all possible efforts to salvage the limb should be made for humanitarian, social and health economic reasons. Surgical reconstruction has traditionally been considered the treatment of choice for SLI but a number of groups now advocate a more liberal use of percutaneous transluminal angioplasty (PTA). Instead of adopting a strategy whereby surgery is routinely attempted in the first instance (and PTA is reserved for those patients who do not have surgically reconstructable disease), a strategy has been adopted whereby PTA is attempted first whenever possible and surgery is reserved for those patients who fail to achieve a satisfactory clinical result. In cases where PTA fails to work and crossover from PTA to surgery is required it has been shown that attempting PTA first did not appear to adversely affect the outcome of subsequent surgical revascularisation. A 'PTA-first' strategy may be preferable because the procedure would appear to be associated with less immediate mortality and morbidity, to be more easily repeated and to cost significantly less than surgery. Furthermore, even though surgery may provide better long-term anatomic patency this may not translate into a superior clinical outcome because patients may not live long enough to reap the potential patency benefits of surgery and, even if a PTA site does reocclude, the limb may remain viable because of the development of collateral vessels. In recent years there has been a dramatic and continuing rise in the number of PTAs being performed for SLI. This increase in activity is not evidence-based and may represent a significant misuse of resources. If the cost-effectiveness of PTA for all or some patients with SLI could be demonstrated then limb salvage might be achieved with less morbidity, mortality and cost than that currently associated with conventional surgery. It has been widely argued that the only way of determining the role of PTA in the management of SLI is by means of randomised, controlled trials comparing PTA and surgery. To date no such studies have been undertaken. The investigators believe that, when conceptualising such a trial, surgery and PTA must not be viewed as competing, but rather as complementary, treatment modalities. The proposed trial is not, therefore, a comparison of the anatomic patency rates of PTA and surgery, but rather a randomised comparison of the effects of two different management strategies ('surgery first' vs 'PTA first') on limb salvage, survival, HRQoL and cost-effective utilisation of NHS resources.

Objective

The objective of the trial is to assess whether, in patients with SLI amenable to PTA, adopting a 'PTA-first' strategy rather than the traditional 'surgery-first' strategy is associated with a better outcome in terms of:

- reduction in all-cause mortality and requirement for major limb amputation (primary end points)
- abolition of symptoms, procedure complications, secondary and crossover interventions, minor amputations, QoL and cost-effective utilisation of NHS resources (secondary end points).

Flow diagram of trial design

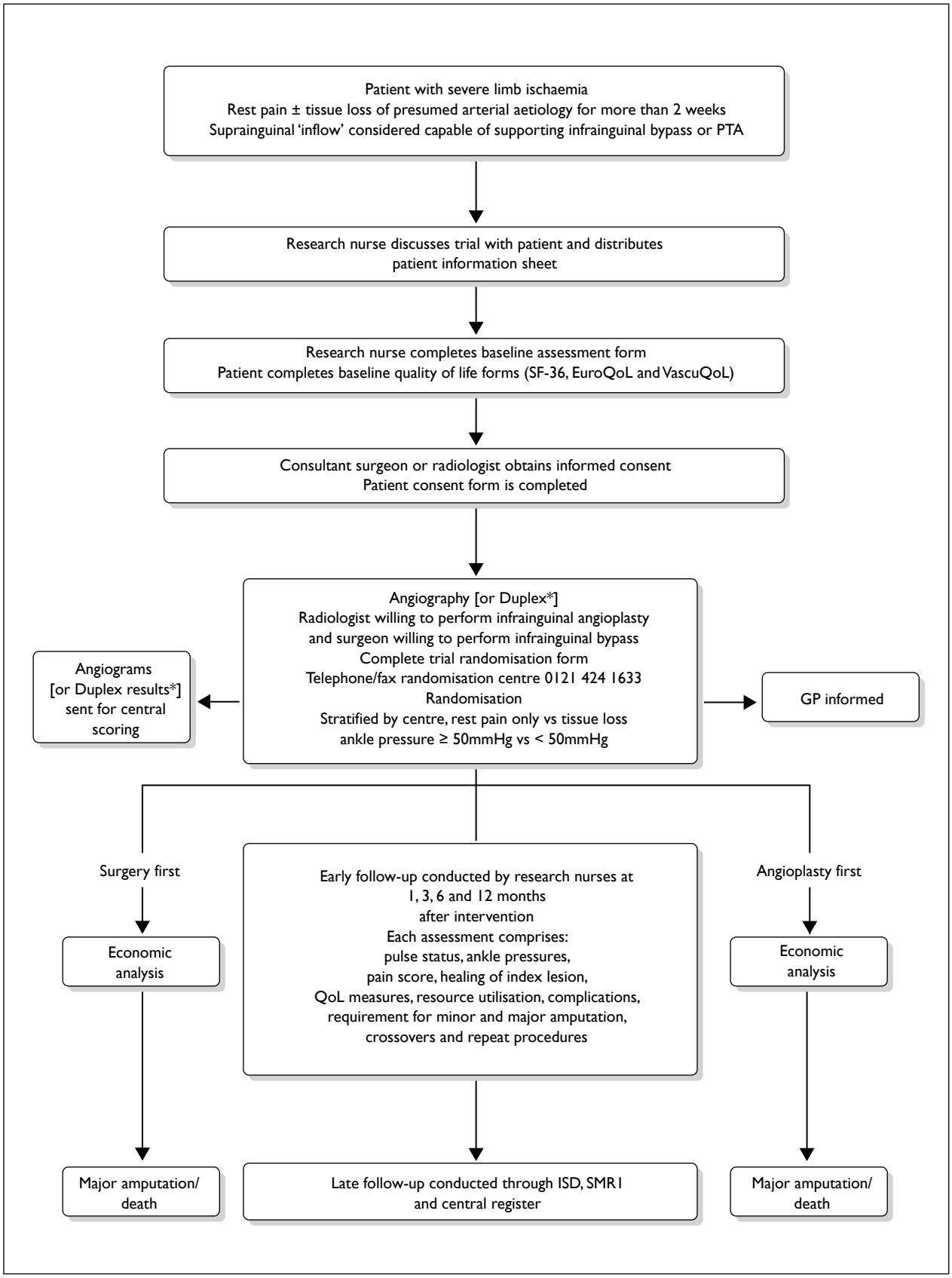


TABLE 63 *Definitions used for groups A to D*

Clinical presentation	Ankle pressure ≥ 50 mmHg	Ankle pressure < 50 mmHg
Rest/night pain only	A	B
Tissue loss ± rest/night pain	C	D

Patient identification

Inclusion criteria

Patients will be inpatients of vascular surgery units situated within participating NHS Trusts. Eligible patients will be those who:

- have severe limb ischaemia on the basis of clinical presentation and ankle pressure as defined by groups A, B, C, D in Table 63
- have adequate suprainguinal 'inflow' to allow either bypass or PTA
- on diagnostic angiography (or duplex), have a pattern of infrainguinal disease that could reasonably be managed either by surgery or PTA in the first instance.

Exclusion criteria

Patients will be excluded if they:

- are unable to give fully informed written consent
- have a degree of limb ischaemia, or a coexisting medical or surgical condition, that makes revascularisation inappropriate.

Brachial and ankle pressure measurement

Brachial and ankle pressures of patients will be measured by the standard sphygmomanometer cuff method. Patients will be stratified on the basis of the highest pressure obtained in any of the three named arteries that can be insonated at the ankle (dorsalis pedis, posterior tibial and perforating peroneal). Patients in which vessel calcification renders the crural arteries incompressible resulting in spuriously high ankle pressures will be stratified on the basis of toe pressure (≥ or < 30 mmHg) if the trial collaborator has access to the required equipment and confidence in the technique. Alternatively, true ankle pressures can be obtained by means of the 'pole' or 'elevation' tests. Patients in whom no arterial signal can be obtained at the ankle will be placed in group B or D.

Absence of suprainguinal disease

Patients must have sufficient arterial 'inflow' at the inguinal ligament for femorodistal bypass or PTA based on the common femoral (or more distal) artery to be performed. Patients who have had pre-existing aortoiliac disease successfully treated will also be eligible for recruitment but the nature and timing of this previous intervention will be noted.

Angiographic pattern of disease and scoring

Angiography will be carried out using the standard techniques used in the participating centres. Following assessment of angiograms by participating clinicians, the angiograms of all patients entered into the trial will be forwarded to the trial headquarters in Birmingham where they will be independently scored by a panel of surgeons and radiologists blind to the treatment received by the patient. In centres where clinical decisions regarding intervention are taken solely on the basis of duplex findings and preintervention diagnostic angiography is not undertaken, duplex results will be used in the place of angiograms.

Blood sample

A blood sample will be taken from each trial patient and analysed for:

- haemoglobin, white cell count and platelet count
- creatinine, glucose, triglyceride and cholesterol.

Patient recruitment

Ethical considerations

The trial will be conducted in accordance with the 'Declaration of Helsinki' (1996 Amendment). The patient information collected will be treated in the strictest confidence. A patient may withdraw from the trial at any point without having to give a reason.

Patient information and baseline assessment

Any patient admitted to hospital with SLI who, in the view of the responsible clinician, is likely to fulfil the entry requirements of the study will be fully informed about the trial by the surgical team or Research Nurse and given a copy of the Patient Information Sheet. A Baseline Assessment Form will be completed by the Research Nurse for

all informed patients as close as possible to the time of admission to the ward. Patients will also be asked to complete Baseline Quality of Life (see Quality of life assessment section, Appendix 1) questionnaires.

Patient consent

Informed patients will be given an adequate amount of time (at least 24 hours) to consider their decision on trial entry. If a patient decides to enter the trial they will be asked to sign a copy of the Patient Consent Form. If a patient does not wish to give informed consent or has a medical condition that makes them unsuitable to enter the trial, the reasons for non-entry will be recorded on their Baseline Assessment Form. Ideally, patient consent will be obtained before angiography but it is recognised that this will not always be possible.

Patient consent can be obtained after angiography but the Patient Consent Form must be completed before randomisation.

Patient recruitment

The final decision to recruit a patient to the trial will be based on the results of angiography (or duplex). It is envisaged that suitable patients will be identified at joint surgical and radiological clinical meetings which are routinely held in most participating centres. In centres where angioplasty is carried out at the time of angiography, patients will be identified at this time.

General practitioner information

A copy of the General Practitioner Information Sheet and Patient Information Sheet will be forwarded to the patient's general practitioner.

Randomisation and treatment

Trial size

A minimum of 450 patients will be recruited with 225 being allocated to each strategy. The sample number calculations propose that 223 patients per treatment arm will be needed for 90% power to detect a 15% difference in 3-year AFS at the 5% significance level. This was based on the assumption that the 3-year AFS in one group might be 50% and in the other group might be 65%.

Randomisation

Following receipt of written informed consent from the patient and angiographic (or duplex) assessment by the responsible radiologist and surgeon, the Trial Randomisation Form will be completed. Patients will be randomised by telephoning or faxing the information to the trial headquarters in Birmingham. At the time of randomisation each patient will be allocated a unique Patient Number which will be used throughout the trial for patient identification.

Treatments

Patients will be treated by either bypass surgery or PTA. Surgeons and radiologists will use their customary techniques. Details of the surgical and PTA techniques used will be documented in Section 1 of the Intervention Form (PTA/Surgery).

Follow-up

Early phase

During hospitalisation any procedure-related complications, further tests and/or periods of time spent in HDU or ITU will be documented on the InPatient Information Form. Records will also be kept of any medications taken by the patient on admission and discharge and analgesia requirements 48 hours before further intervention, discharge or primary end point. Before discharge of trial patients, pulse status, brachial and ankle pressures and healing status of index lesion (in those patients with tissue loss) will be recorded. During the first 6 months after intervention patients will be followed by the Research Nurse in each area. Assessments will take place at 1, 3 and 6 months (± 1 week) in a hospital-based clinic or, when necessary, by a home visit and information recorded on a One-Month Clinical Follow-up or Clinical Follow-up Form (for 3 and 6 months).

Further intervention

In the event that failure of the primary intervention leads to deterioration in clinical status such that further intervention is required then the nature of that secondary intervention (PTA/Surgery/Amputation) will be left to the judgement of the responsible surgeon and radiologist. Details of any further interventions will be recorded on the relevant Intervention Form (PTA/Surgery/Amputation).

Late phase

Patients will undergo a final clinical follow-up by the Research Nurses in each area in a hospital based clinic 12 months after intervention. From 12 months onwards, unless the patient experiences a clinical end point such as an additional procedure or amputation, the patient will be discharged from the Research Nurses follow-up and return

to normal clinical care. Notification of any death, interventions and discharges from hospital during the remainder of the trial period will be provided by the Information and Statistics Division of the National Health Service in Scotland using record linkage to Scottish Morbidity Records (SMR1) and General Registrar Office (Scotland) [GRO(S)] death records (or in England, regional hospital discharge statistics or individual trusts involved in the trial), general practitioners and the National Health Service Central Register.

Interim analysis of study results

During the study, interim analyses of mortality and adverse clinical events will be supplied to the Chairman of the Data Monitoring Committee at a frequency to be determined by that committee. The committee will advise the investigators and the Steering Committee if, in their view, continued use of either intervention is clearly indicated or contraindicated in terms of a net difference in all-cause mortality, limb loss or adverse clinical events.

Quality of life assessment

Quality of life assessments

Both generic and disease-specific instruments will be used to measure patients' perceptions of the severity of their condition and the outcome of intervention. Self-completed questionnaires will be distributed and collected from patients by the Research Nurses at the hospital-based clinics up to 12 months after primary intervention. After this period, patients will be sent questionnaires through the post and asked to return them after completion.

Timing of assessments

The QoL assessments will be conducted at:

- baseline to assess the impact of the disease on QoL and to allow comparison of the two groups
- 3, 6 and 12 months (± 1 week) and then annually until the end of follow-up.

Generic instrument

Two generic instruments will be used:

- the Short-Form 36 (SF-36) questionnaire
- the EuroQoL-5D (EQ-5D) questionnaire.

Disease-specific instrument

The VascuQoL questionnaire, recently developed at King's College, London to measure QoL in patients with leg ischaemia, will be used.

Health economic assessment

Economic evaluation

The cost-effectiveness of PTA versus reconstructive surgery for SLI will be conducted using well-established criteria for the design, execution and reporting of economic evaluations. Costs will be identified, measured and valued from the perspective of the NHS and the patient.

Resource data

NHS costs

Information will be recorded for all patients regarding:

- the time taken and personnel present at the intervention procedure (Intervention Form: Section 1)
- the time spent in hospital and the type of care received (Inpatient Information Form: Section 1).

Detailed information will also be collected from at least five patients undergoing each intervention in all participating centres regarding the resources used during the intervention procedure in terms of materials used and medications administered (Intervention Form: Sections 2 and 3).

Patient costs

Costs incurred in the hospital setting will be supplemented with patient self-reported data on primary-care consultations and receipt of community-health services (One-Month Clinical Follow-up Form and Clinical Follow-up Form).

Unit costs will be attached to all episodes of care and costs borne by patients to generate a monetary estimate of resource consequences.

Results

These profiles of service utilisation will be used to model the resource consequences and likely effects of the two management regimes. Results will be presented in terms of the incremental cost per additional life-year gained over a range of time horizons from 3 to 10 years. The cost-effectiveness design will enable an assessment of the net costs (i.e. costs of PTA or reconstructive surgery less averted costs of revascularisation and/or amputation).

Statistical analysis

Final analysis

The two randomised groups will be compared at baseline using appropriate summary statistics.

The primary effect analysis will be performed on an intention-to-treat basis, and will use a log-rank test to compare the time to the first trial end point (death or limb loss). The robustness of the results of this comparison will be assessed using the Cox proportional hazards regression model to adjust for key baseline covariates. The results will be summarised by presenting the estimated relative hazard, along with the 95% confidence intervals.

Results will also be examined for 'completers only' because of the likely crossover between groups and the requirement for further procedures of the same type in each group. Costs analysis will be based on recorded resource usage by patients for a minimum of 2 years after intervention or until death within a minimum follow-up period of 2 years. Although major limb amputation is a primary end point, the costs incurred by patients after amputation will also be included in the analysis because they represent a major use of NHS resources.

Trial milestones

July 1999	appointment of Research Nurses in south-east and south-west Scotland
	begin pilot study of patient recruitment in Edinburgh and Glasgow
August 1999	participants' meeting to discuss and finalise trial protocol and documentation
	Steering Committee and Data Monitoring Committee to meet and confirm the 'stopping rules'
September 1999	(month 7) commence patient recruitment in all trial regions
February 2000	(month 12) 50 patients recruited
February 2001	(month 24) 100 patients recruited; 50 patients completed 6-month follow-up
August 2001	(month 30) 150 patients recruited; 100 patients completed 6-month follow-up
February 2002	(month 36) 250 patients recruited; 150 patients completed 6-month follow-up
	interim analysis by the Data Monitoring Committee
	second participants' meeting
	200 angiograms independently scored
August 2002	(month 42) 350 patients recruited; 250 patients completed 6-month follow-up
	300 angiograms independently scored
February 2003	(month 48) 450 patients recruited; 350 patients completed 6-month follow-up
	400 angiograms independently scored
	interim data analysis by the Data Monitoring Committee
	end of recruitment
August 2003	(month 54) 450 patients completed 6-month follow-up
	450 angiograms independently scored
February 2004	(month 60) 450 patients followed for a mean of 30 months
August 2004	(month 66) 450 patients followed for a mean (range) of 36 (24–48) months
February 2005	(month 72) – end of trial
	analysis of data
	submission of draft paper suitable for publication in a peer-reviewed journal
	submission of draft report
	dissemination of findings

Statistical analysis – revised protocol

This was produced by Professor Gillian Raab and Mrs Helen Storkey on 21 September 2005.

Analysis plan – general

All data cleaning and model investigations (as described below) will be carried out without reference to the data on treatment allocations.

The analyses of the effects of treatments will not be run until just before 6 October 2005, so that those in the writing group can see it together. STRICT CONFIDENTIALITY OF RESULTS WILL BE MAINTAINED AFTER THAT AND BEFORE PUBLICATION.

Major outcomes – intention-to-treat analyses

- primary outcome: amputation-free survival
- secondary outcome: time to death.

These will be analysed by intention to treat, using the date of randomisation as a zero of time.

Both outcomes will be presented as Kaplan–Meier survival curves. A table of numbers at risk will be presented below the survival curve, with the time points being 6 months, 1, 2 and 3 years. An analysis of differences in person-years using areas above the survival curves may be presented, depending on the outcome.

Statistical analysis will consist of:

- chi-squared tests comparing randomised groups in terms of their survival to 6 months and 1 year and (perhaps) 3 years; for 3 years and perhaps 1 year the comparison will be

based on a life-table estimate rather than a simple chi-squared test
- Cox proportional hazards regression over the whole period (model a) and with separate treatment effects defined in the period 0–6 months and 6 months onwards (model b).

The proportional hazards analysis will be adjusted for the following baseline covariates:

- stratification groups (B and D combined) (time dependent in two periods)
- smoking: never smoker, current-smoker, ex-current
- log-creatinine
- age (continuous)
- gender
- statin use at baseline
- diabetes (Yes/No)
- body mass index (grouped) with missing as one of the categories.

For cases with log-creatinine the 21 missing values will be replaced by imputed values predicted from other covariates (statin use and smoking status were the predictive variables).

For analyses of separate treatment effects (model b) all covariates will be allowed to affect survival differently in periods before 6 months and after 6 months.

The purpose of the covariates for survival analysis is that we can make more precise comparisons if we do it within homogeneous groups.

Treatment by covariate interactions will be investigated for the following factors:

- three stratification groups
- diabetes
- log-creatinine (above/below the median)
- a risk score calculated from a model for survival that excludes the treatment.

Interaction tests will be run for models a and b. For model b, the risk scores that are specific to each time period will be used in calculating risk scores from a model for survival that excludes the treatment.

For the analyses with the risk score the model will include risk score and treatment and their interaction only, because the risk score will stand in for all the other variables.

On-treatment analysis

Thirty-day mortality and 30-day morbidity (complications as asked include further hospital admission, stroke, myocardial infarction) by the two treatments, by the treatments received and using time from the intervention. This will also be broken down according to treatments received (allocated or opposite) at various time periods from randomisation. Time periods and categories will be determined following exploratory analyses of the whole population.

Similar analyses will be presented for the following outcome:

- reintervention rate by two groups: (1) further surgery and (2) further angioplasty.

Appendix 2

Statistical plan for extended follow-up 2005–8

Short- and medium-term results of the BASIL trial

The short-term and medium-term findings of the BASIL trial were published in 2005.[50]

This intention-to-treat analysis indicated that, in patients presenting with SLI [evidenced by rest/night pain with or without tissue loss (ulceration/gangrene)], up to 2 years from randomisation, 'bypass-surgery-first' and 'balloon-angioplasty-first' strategies are associated with similar outcomes in terms of the main clinical end points (PEPs) [AFS, ACM (or OS) and HRQoL]. Although the short-term mortality associated with each strategy was similar, surgery was associated with significantly higher morbidity and angioplasty with a significantly higher failure and reintervention rate, often resulting in a need to cross over to surgery to save life and limb. Up to 1 year, a 'bypass-surgery-first' strategy was approximately one-third more expensive. An exploratory analysis, which was not in the statistical protocol, and was carried out after the survival curves had been studied, suggests that patients who survive with their trial limb intact out to 2 years from randomisation are more likely to remain alive with their trial limb intact if they had originally been randomised to a 'bypass-surgery-first' strategy. Although this difference was highly statistically significant, this was a post-hoc analysis based on a relatively small number of end points after 2 years. This is a very important finding that, if confirmed by longer-term follow-up, would have a major impact on clinical practice worldwide because it would suggest that for the great majority of patients expected to live more than 2 years, bypass surgery rather than angioplasty is the preferred treatment in terms of preserving life and limb. Such an important clinical benefit is likely to be matched by improved HRQoL and may be associated with a reduction in costs as the single largest cost burden in this patient group is likely to be amputation.

Methods for the follow-up study and assessment of its power

Methods

Further follow-up will be carried out and will allow us to judge if the apparent long-term superiority of a 'bypass-surgery-first' strategy is real and clinically meaningful, or just a chance finding. The power of the follow-up study is based on information available from new events observed during extended follow-up without taking into account the cases who contributed events and follow-up to the analysis presented in the report of the interim analysis.[50] If these new data, taken by themselves, indicate that a 'balloon-angioplasty-first' strategy is associated with poorer long-term outcome in terms of AFS and ACM, then their combination with data from the interim analysis,[50] presented in the Lancet, will provide very convincing evidence of the clinical superiority of surgery over angioplasty. We know the direction we expect for the difference, so we propose to use a one-sided test (see below).

Model used for power calculations

In the interim analysis,[50] the analysis of the data on survival to PEP was, appropriately, carried out using a Cox proportional hazards model, and this will be the final model used for the extended follow-up results. For the power calculations, a simpler model using a person-years approach is used. First, we present the data collected so far analysed by this method. The number of person-years of follow-up over the period from 2 years after randomisation to either the PEP (AFS, ACM) or the end of the follow-up period and the PEP events observed are shown in Table 64.

The ratio of the event rates is 2.3, which is very similar to the hazard ratio of 2.7 obtained from the Cox model. The difference in rates is also highly significant: difference 0.112 (95% CI 0.014 to 0.210); agreeing, as expected, with the results obtained from the Cox model.

Simulation of further follow-up

A parametric survival model (Weibull) is used to simulate the information that will come from further follow-up. The parameters of the model are based on models fitted to the data up to the 2005 analysis. All patients who had not yet reached a PEP, and who were not lost to follow-up, (n = 241, 115 angioplasty, 126 surgery) had a time to PEP simulated from a conditional Weibull distribution, given the survival so far, and right truncated to

TABLE 64 *Person-years analysis for the period beyond 2 years after randomisation*

Strategy	Number of patients followed beyond 2 years	Person-years of follow-up	PEPs	Rate of PEPs per person-year
Balloon angioplasty first	100	115	23	0.201
Bypass surgery first	108	135	12	0.089

PEPs, primary end points; namely, AFS and ACM.

the age of 100 (or 5 years post-randomisation if longer) to avoid a few extreme survivals produced by the model. The simulation was based on the assumption of no difference between the treatments. The OS curve used in the simulation is illustrated in Figure 32. The dotted line shows the part extrapolated beyond the current data.

The simulation was based on the assumption of a common risk of reaching a PEP for both treatments.

The events occurring after 2 years of follow-up for the two treatments were then adjusted to correspond to the random events that would be generated when the rate ratio had a series of values (see Table 65).

A person-years' analysis was then carried out for the simulated data along the lines of that presented for the current data above. Follow-up time was only counted if it was after the first analysis, at least 2 years from randomisation, and within the time when it would have occurred within the extra follow-up years.

Various possible choices of the extra follow-up time were investigated and 2.5 years was considered appropriate. The results for 2.5 years are shown in Table 64.

The rate ratio found for data so far was 2.3. We can see that by using 2.5 years of additional follow-up, we will have very good power to detect an effect size comparable to that found already, and a very reasonable power to detect smaller effect sizes. This good power is essential for several reasons:

- because of the post-hoc nature of the first analysis, it may overestimate the true rate ratio
- some of further follow-up will be at older ages than the original data, so the effect due to the treatments may be less pronounced if other causes of mortality are also contributing
- the model used to calculate sample numbers includes some extrapolation where the assumptions cannot be checked so it is possible that actual event rates may be lower than those shown.

We recognise that the use of a one-sided test in these power calculations may be controversial but we believe it is justified in these circumstances. Should those refereeing this application feel it is not justified, then we would require approximately a further 6 months of funding and follow-up (3

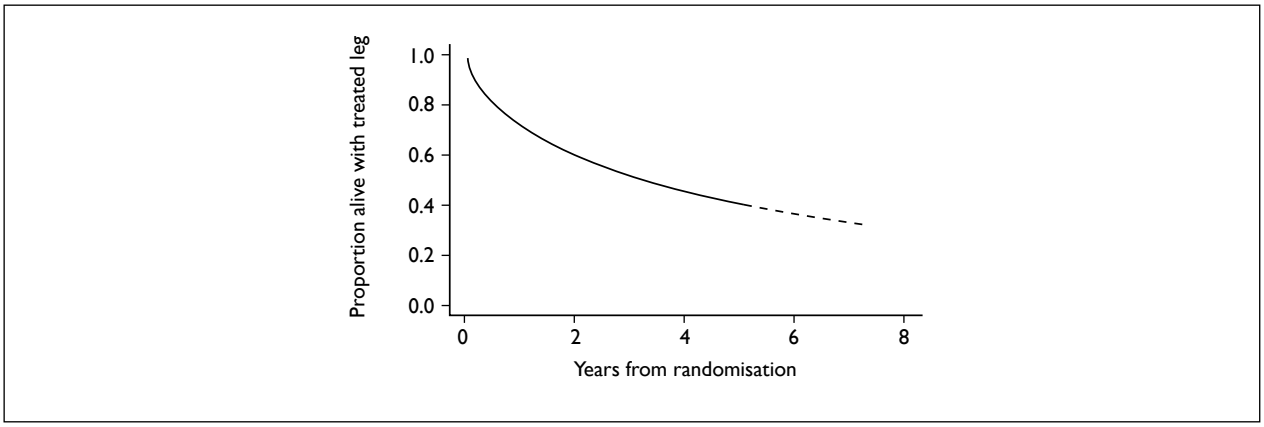


FIGURE 32 *Overall survival curve used in the Weibull simulation.*

TABLE 65 *Power to detect a treatment difference at 2 years+ from randomisation with 2.5 years of extra follow-up, using new follow-up data only; results from 1000 simulations in each case*

Rate ratio (angioplasty/surgery) True effect rate used in simulation	Expected number of events during the extra follow-up time		Rate of events during extra follow-up for period 2 years+ from randomisation		Power to detect rate difference
	Angioplasty first	Surgery first	Angioplasty first	Surgery first	
1.0	34	37	0.15	0.15	5%
1.25	37	33	0.17	0.14	24%
1.5	40	29	0.19	0.12	55%
1.75	44	28	0.20	0.11	77%
2.0	47	26	0.22	0.11	90%
2.3	50	24	0.23	0.10	96%

years in total) to obtain equivalent power for a two-sided test. For the great majority of patients, whose data were censored for the interim analysis[50] at 28 February 2004, 2.5 years extra follow-up will mean follow-up until 30 August 2007.

The survival to the PEP and to death will be carried out in the same manner as was used for the interim analysis.[50] We also plan to carry out further on-treatment analyses that will describe the patient journeys of the patients in terms of success rates of procedures and subsequent interventions. Some of the analyses of the original data that are currently under way suggest that we may be able to identify patient characteristics that affect the details of the journey. Further follow-up will allow us to extend this analysis with the aim of making further recommendations as to the type of patient who may benefit from different types of treatments. These follow-up data are now available and have been cleaned and organised. Preliminary modelling and checking has been carried out (but without reference to the variable giving treatment allocation). The detailed section that follows specifies exactly how the treatment comparisons will be carried out.

Statistical analysis without use of treatment data

Analysis plan – general

All data cleaning and model investigations (as described below) will be carried out without reference to the data on treatment allocations. The analyses of the effects of treatments will not be run until this protocol has been agreed with all authors, so that those in the writing group can see it together. STRICT CONFIDENTIALITY OF RESULTS WILL BE MAINTAINED AFTER THAT AND BEFORE PUBLICATION.

Summary of additional data follow-up available

The PEP of the 2005 analyses was defined as survival without major amputation of the trial leg (AFS) with survival to death as a secondary end point. After the analysis for the interim analysis[50] there were 289 of the 452 randomised patients still alive. During the additional follow-up to 2007, 87 of these patients died. There were also six further amputations, two of which were patients who subsequently died. Details are in Table 66.

We have 78 PEPs (72 deaths and six amputaions), in line with the simulation study reported above. However, we will have better power to look at new deaths in follow-up, because we can then include the 39 patients and 13 more deaths for those who were alive with amputations at the 2005 analysis. In early periods we will have better power for AFSs and in later periods better power for deaths. Despite this, because the major focus of the BASIL trial has always been AFS, we will continue to use death or major amputation of the trial as the PEP, as before. Analyses of time to death will also be carried out.

Angiogram data

In addition to the additional follow-up data we have also been able to collate the information from the angiogram assessments of all patients with angiograms available (all but 34 cases). These were scored in two ways. In the first case detailed Bollinger scoring[52] was carried out for all arteries in the leg (see Chapter 6). This was performed independently by two observers and a consensus score was obtained for each segment. The data were then summarised as an upper mean score (average of segments down to the distal popliteal segment) and a lower mean score for those below.

TABLE 66 *Status in 2005 by status in 2007 for those alive at 2005*

	Status in 2005		
Status in 2007	**Alive no amputation**	**Alive with amputation reported**	**Total**
Alive no amputation	172	0	172
Alive with amputation	4	26	30
Total alive	176	26	202
Amputation then death	2	13	15
Death	72	0	72
Total deaths 2005–7	74	13	87
Total	250	39	289

This table includes those previously noted as lost-to-follow-up, some of whom have now come back in to follow-up because either their deaths were reported or they were traced at one of the BASIL hospitals. A few of these may be excluded from the final analysis once the final data checking is complete.

In the second case, the angiogram assessments were scored according to the TASC II criteria.[51]

Analyses of additional follow-up, without reference to treatment

A Cox proportional hazards analysis has been performed to investigate which factors (including the angiogram scores) are predictive of AFS and OS. The following factors were significantly associated with survival:

- BASIL randomisation stratification group
- below-knee Bollinger angiography score
- above-knee Bollinger angiography score
- BMI (four groups: underweight, worst, heaviest, best)
- age (as a continuous variable)
- diabetes (either type)
- creatinine (three groups: middle is best, high is worst, low is intermediate)
- smoking (ex-smokers best, continuing smokers worst).

Missing data were including by assigning them to a separate category [angiography scores (34 cases), body mass index (85 cases) and log creatinine (21 cases)].

Each of these factors was assessed to see if their effect varied over time using a method that correlates the survival analysis residuals with time.[217] Only the upper angiography score was shown to have an effect on survival that was time dependent. This operated only in the first period (approximately to 2 years) after randomisation.

The final predictive model therefore included the factors mentioned above and a time-dependent factor for the upper angiography score that changed 2 years from randomisation.

Protocol for analysis of treatment effects

Main intention-to-treat analysis

- Primary outcome: AFS
- Secondary outcome: death from all causes.

Although we will retain the same outcomes, formally, as in the preceding analysis we expect to present an integrated conclusion based on the combined data in the report of this study. These will be analysed by intention to treat, using the date of randomisation as time zero. Both outcomes will be presented as Kaplan–Meier survival curves. A table of numbers at risk will be presented below the survival curve, with the time points being 1, 2 and 3, 4 and 5 years.

Statistical analysis will consist of

- Cox proportional hazards regression with separate treatment effects defined in the period 0–2 years and 2 years onwards. The effect of treatment in the second period will be tested for significance against no effect (primary test), and will also be compared with the treatment effect in the first period.
- An analysis of the additional events and follow-up time since the 2005 analysis and particularly the events (PEPs and deaths) and follow-up from 2 years beyond randomisation. If this

additional data, by itself, provides evidence of a higher event rate for those assigned to bypass (one-sided test) then it will be strong evidence that the previously identified trend was not due to chance.
- The Cox proportional hazards analysis with adjustment for the covariates specified in the prediction model in Chapter 3 including those used in the previous analyses, and the Bollinger and TASC scores.

If we find that the effect of treatments in the second period is reduced on adjustment for covariates then it could be interpreted as showing that those surviving to 2 years, following bypass surgery, are a fitter group.

If the treatment difference found in the previous analysis is found to be maintained then the following interactions will be examined for their influence on treatment in the first and second time periods separately. Treatment by covariate interactions in the time periods (< 2 years, ≥ 2 years) will be investigated for the following factors:

- three stratification groups
- angiography scores
- a risk score calculated from a model for survival to PEP and to death that excludes the treatment (as described on the previous page).

These, and only these, interactions will be examined initially for time to PEP and for time to death. Any other interactions found from subsequent analyses will be considered exploratory. We acknowledge that there will be only modest power (at best) to examine the selected interactions but they are important because they may help to explain our findings. If a treatment difference is found by the Cox proportional hazards analysis, described above, the results of these analyses (effectively comparing the treatment difference by initial characteristics) will be presented. The evidence from this study of the potential benefit of these two treatments for patients identified according to their baseline characteristics will be described. These results will be presented as effects (e.g. survival rates to various points in time) by subgroup and confidence intervals for the corresponding treatment differences.

On-treatment analysis

This will only be carried out if the analysis just described shows a significant treatment difference in the second period. The outcomes in terms of survival and amputation will be compared according to the treatments received in each of the periods after randomisation. A detailed analysis will be carried out that describes the treatments received by patients up to 3 years after randomisation when almost all the patients have complete follow-up. Every attempt will be made to understand the predictors of the outcomes and further exploratory analyses may be carried out.

In addition we would expect to investigate more fully the form of the hazard function for each treatment group, to make sure that 2 years was the most reasonable choice for modelling these data. Based on this we will expect to develop predictive models that will incorporate the two stages of survival (to amputation, if this happens) and to death, or a single stage if no amputation, and also to investigate survival by cause of death.

Appendix 3
BASIL trial forms

Baseline Assessment Form

(To be completed by Research Nurse prior to randomisation. Please complete text in BLOCK CAPITALS, tick the appropriate box or enter numbers into the boxes provided.)

Date of Admission: ☐☐/☐☐/☐☐ (dd/mm/yy).

Date of Assessment: ☐☐/☐☐/☐☐ (dd/mm/yy).

Centre Name: _____ Centre Number: ☐☐

Recruiting Consultant: _____

Full Name of Patient: _____

Patient's Address: _____

_____ Telephone No.: _____

Patient's Full Post Code: ☐☐☐☐/☐☐☐

Patient's Date of Birth: ☐☐/☐☐/☐☐

Gender: MALE ☐ FEMALE ☐

GP Name: _____

GP Address: _____

_____ Telephone No.: _____

Trial Leg: RIGHT ☐ LEFT ☐

Risk Factors

Smoking: NEVER SMOKED ☐

CURRENT ☐ No. of years smoked: ☐☐
No. of cigarettes per day: ☐☐

EX-SMOKER ☐ No. of years smoked: ☐☐
Years since last cigarette: ☐☐

Diabetes: NO ☐ INSULIN DEPENDENT ☐ NON-INSULIN DEPENDENT ☐

Hypercholesterolaemia: NO ☐ YES - UNTREATED ☐ YES - TREATED ☐

Hypertension: NO ☐ YES - UNTREATED ☐ YES - TREATED ☐

Patient Mobility

Independent ☐ Cane/Walker ☐ Prosthesis ☐ Wheelchair ☐ Bed-bound ☐

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Baseline Assessment Form **Case Reference No:** _____

Past Medical History

Previous MI: NO ☐ YES ☐

Angina: NO ☐ YES - ON EXERCISE ☐ YES - AT REST ☐

TIA: NO ☐ YES ☐

Stroke: NO ☐ YES ☐

Other: _____

Previous intervention to trial leg: NO ☐ YES ☐

If YES: PTA ☐ Stent ☐ Surgery ☐ Digital/Forefoot Amputation ☐
Supra-inguinal ☐ Infra-inguinal ☐

Is the other leg symptomatic? NO ☐ YES ☐

If YES: Intermittent Claudication ☐ Severe Limb Ischaemia ☐
Category: A ☐ B ☐ C ☐ D ☐

Previous intervention to other leg: NO ☐ YES ☐

If YES: PTA ☐ Stent ☐ Surgery ☐
Amputation ☐: Digits ☐ Forefoot ☐ Trans-tibial ☐ Trans femoral ☐

Clinical Status

Patient's height (cm): ☐☐☐ Patient's weight (kg): ☐☐☐ Pulse: ☐☐☐

Brachial blood pressure: Right: ☐☐☐/☐☐☐ Left: ☐☐☐/☐☐☐

Ankle pressures in trial leg: *(insert not found* **[NF]** *if no signal insonated)*
for patients with compressible vessels record cuff pressure: for patients with incompressible ankle vessels record toe pressure or height (cm) above bed where Doppler signal lost (pole test)

	Cuff pressure	**or**	Height (cm) above bed
Dorsalis pedis	☐☐☐ mmHg		☐☐☐ = ☐☐☐ mmHg
Posterior tibial	☐☐☐ mmHg		☐☐☐ = ☐☐☐ mmHg
Perforating peroneal	☐☐☐ mmHg		☐☐☐ = ☐☐☐ mmHg
Toe pressure	☐☐☐ mmHg		

Ankle:brachial pressure index in trial leg = ☐.☐☐
(highest ankle pressure/highest brachial pressure)

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Baseline Assessment Form **Case Reference No:** _____

Is femoral pulse detectable? NO ☐ YES ☐

Pattern of tissue loss

(* - *circle appropriate category*)

Rest/night pain NO ☐ YES ☐

Ulcer NO ☐ YES ☐ - Toes / Forefoot / Hindfoot / Ankle*

- Size of ulcer ☐☐ cm^2

Gangrene NO ☐ YES ☐ - Toes / Forefoot / Hindfoot / Ankle*

Medication on admission

Drug name	Dose/unit	Frequency

Blood sample taken NO ☐ YES ☐ - Date ☐☐/☐☐/☐☐

Randomisation

Did patient give consent for randomisation NO ☐ YES ☐

If YES, was patient randomised NO ☐ YES ☐

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

If NO, why was patient not randomised?

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Baseline Assessment Form **Case Reference No:** _____

Blood test results on admission

(* delete as necessary. Please enter ND if analysis is not done)

	Test Result (Please include units)	**Date of Tests**
Haemoglobin:	_____	☐☐/☐☐/☐☐
White cell count:	_____	
Platelet count:	_____	
Creatinine:	_____	
Fasting/Random* glucose:	_____	
Fasting/Random* triglyceride:	_____	
Total cholesterol:	_____	

Other Tests (please specify):

	_____	☐☐/☐☐/☐☐
	_____	☐☐/☐☐/☐☐
	_____	☐☐/☐☐/☐☐

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
One-MonthClinical Follow-up Form

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

One–Month Clinical Follow-up Form

(To be completed by Research Nurse. Please complete text in BLOCK CAPITALS, tick the appropriate box or enter numbers into the boxes provided.)

Date of Assessment: ☐☐/☐☐/☐☐ (dd/mm/yy)

Recruiting Consultant: _____

Patient's Date of Birth: ☐☐/☐☐/☐☐ (dd/mm/yy) Gender: MALE ☐ FEMALE ☐

Trial Leg: LEFT ☐ RIGHT ☐

Date of Primary Intervention: ☐☐/☐☐/☐☐ (dd/mm/yy)

Type of Primary Intervention: PTA ☐ SURGERY ☐

Further Interventions: NONE ☐ PTA ☐ SURGERY ☐ AMPUTATION ☐

Dates of Further Interventions: ☐☐/☐☐/☐☐ ☐☐/☐☐/☐☐

Clinical status

Pulse: ☐☐☐

Brachial blood pressure: Right: ☐☐☐/☐☐☐ Left: ☐☐☐/☐☐☐

Ankle pressures in trial leg: *(insert not found* **[NF]** *if no signal insonated)*
for patients with compressible vessels record cuff pressure: for patients with incompressible ankle vessels record toe pressure or height (cm) above bed where Doppler signal lost (pole test)

	Cuff pressure	**or**	Height (cm) above bed
Dorsalis pedis	☐☐☐ mmHg		☐☐☐ = ☐☐☐ mmHg
Posterior tibial	☐☐☐ mmHg		☐☐☐ = ☐☐☐ mmHg
Perforating peroneal	☐☐☐ mmHg		☐☐☐ = ☐☐☐ mmHg
Toe pressure	☐☐☐ mmHg		

Ankle:brachial pressure index in trial leg = ☐.☐☐
(highest ankle pressure/highest brachial pressure)

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
One-MonthClinical Follow-up Form

Patient Mobility

Independent ☐ Cane/Walker ☐ Prosthesis ☐ Wheelchair ☐ Bed-bound ☐

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

Pattern of tissue loss

Rest Pain:	ABSENT	☐	IMPROVED	☐	UNCHANGED	☐
	WORSE	☐	NA	☐	AMPUTATION	☐
Ulceration:	HEALED	☐	IMPROVED	☐	NO CHANGE	☐
	WORSE	☐	NA	☐	AMPUTATION	☐
Gangrene:	ABSENT	☐	IMPROVED	☐	NO CHANGE	☐
	WORSE	☐	NA	☐	AMPUTATION	☐

(NA = Not Applicable)

Complications

(occurring since discharge from hospital)

Complication		
New onset or worsening of angina	NO ☐	YES ☐
Myocardial infarction	NO ☐	YES ☐
TIA / amaurosis fugax	NO ☐	YES ☐
Stroke	NO ☐	YES ☐
Haematoma (no surgical drainage required)	NO ☐	YES ☐
Haematoma (surgical drainage required)	NO ☐	YES ☐
Wound infection (requiring antibiotics)	NO ☐	YES ☐
Chest infection (requiring antibiotics)	NO ☐	YES ☐
Urine infection (requiring antibiotics)	NO ☐	YES ☐
False aneurysm (not requiring surgical repair)	NO ☐	YES ☐
False aneurysm (requiring surgical repair)	NO ☐	YES ☐
Surgical intervention for other complication	NO ☐	YES ☐

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
One-MonthClinical Follow-up Form

Other (please specify):

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

Patient Health

Since the last visit has the patient had:

Any in-patient hospital admissions? NO ☐ YES ☐ NUMBER ☐☐

Episode 1

Date of admission: ☐☐/☐☐/☐☐ (dd/mm/yy)
Date of discharge: ☐☐/☐☐/☐☐ (dd/mm/yy)

Principal/main diagnosis: _____

Secondary/other diagnosis: _____

Surgical operations/procedures: _____

_____

Episode 2

Date of admission: ☐☐/☐☐/☐☐ (dd/mm/yy)
Date of discharge: ☐☐/☐☐/☐☐ (dd/mm/yy)

Principal/main diagnosis: _____

Secondary/other diagnosis: _____

Surgical operations/procedures: _____

_____

Episode 3

Date of admission: ☐☐/☐☐/☐☐ (dd/mm/yy)
Date of discharge: ☐☐/☐☐/☐☐ (dd/mm/yy)

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
One-MonthClinical Follow-up Form

Principal/main diagnosis: _____

Secondary/other diagnosis: _____

Surgical operations/procedures: _____

_____

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
One-MonthClinical Follow-up Form

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

Any day case admissions?	NO ☐	YES ☐	NUMBER ☐☐
Any outpatient attendances?	NO ☐	YES ☐	NUMBER ☐☐
Any GP consultations?	NO ☐	YES ☐	NUMBER ☐☐
Any practice nurse consultations?	NO ☐	YES ☐	NUMBER ☐☐
Any community nurse visits?	NO ☐	YES ☐	NUMBER ☐☐

Analgesia Requirement

Please record the patients analgesia requirements over the previous 48 hours:

Drug	Total Dose

Additional information:

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Clinical Follow-up Form

PATIENT NUMBER ☐☐/☐☐☐☐/☐

Clinical Follow-up Form

(To be completed by Research Nurse. Please complete text in BLOCK CAPITALS, tick the appropriate box or enter numbers into the boxes provided.)

Date of Assessment: ☐☐/☐☐/☐☐ (dd/mm/yy)

Time of Assessment: 3/12 ☐ 6/12 ☐ 12/12 ☐

Recruiting Consultant: _____

Patient's Date of Birth: ☐☐/☐☐/☐☐ (dd/mm/yy) Gender: MALE ☐ FEMALE ☐

Trial Leg: LEFT ☐ RIGHT ☐

Date of Primary Intervention: ☐☐/☐☐/☐☐ (dd/mm/yy)

Type of Primary Intervention: PTA ☐ SURGERY ☐

Further Interventions: NONE ☐ PTA ☐ SURGERY ☐ AMPUTATION ☐

Dates of Further Interventions: ☐☐/☐☐/☐☐ ☐☐/☐☐/☐☐

Clinical status

Pulse: ☐☐☐

Brachial blood pressure: Right: ☐☐☐/☐☐☐ Left: ☐☐☐/☐☐☐

Ankle pressures in trial leg: *(insert not found* **[NF]** *if no signal insonated)*
for patients with compressible vessels record cuff pressure: for patients with incompressible ankle vessels record toe pressure or height (cm) above bed where Doppler signal lost (pole test)

	Cuff pressure	**or**	Height (cm) above bed
Dorsalis pedis	☐☐☐ mmHg		☐☐☐ = ☐☐☐ mmHg
Posterior tibial	☐☐☐ mmHg		☐☐☐ = ☐☐☐ mmHg
Perforating peroneal	☐☐☐ mmHg		☐☐☐ = ☐☐☐ mmHg
Toe pressure	☐☐☐ mmHg		

Ankle:brachial pressure index in trial leg = ☐.☐☐
(highest ankle pressure/highest brachial pressure)

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Clinical Follow-up Form

Patient Mobility

Independent ☐ Cane/Walker ☐ Prosthesis ☐ Wheelchair ☐ Bed-bound ☐

PATIENT NUMBER ☐☐/☐☐☐☐/☐☐

Pattern of tissue loss

Rest Pain:	ABSENT	☐	IMPROVED	☐	UNCHANGED	☐
	WORSE	☐	NA	☐	AMPUTATION	☐
Ulceration:	HEALED	☐	IMPROVED	☐	NO CHANGE	☐
	WORSE	☐	NA	☐	AMPUTATION	☐
Gangrene:	ABSENT	☐	IMPROVED	☐	NO CHANGE	☐
	WORSE	☐	NA	☐	AMPUTATION	☐

(NA = Not Applicable)

Patient Health

Since the last visit has the patient had:

Any in-patient hospital admissions? NO ☐ YES ☐ NUMBER ☐☐

Episode 1

Date of admission: ☐☐/☐☐/☐☐ (dd/mm/yy)
Date of discharge: ☐☐/☐☐/☐☐ (dd/mm/yy)

Principal/main diagnosis: _____

Secondary/other diagnosis: _____

Surgical operations/procedures: _____

_____

Episode 2

Date of admission: ☐☐/☐☐/☐☐ (dd/mm/yy)
Date of discharge: ☐☐/☐☐/☐☐ (dd/mm/yy)

Principal/main diagnosis: _____

Secondary/other diagnosis: _____

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Clinical Follow-up Form

Surgical operations/procedures: _____

_____

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

Episode 3

Date of admission: ☐☐/☐☐/☐☐ (dd/mm/yy)
Date of discharge: ☐☐/☐☐/☐☐ (dd/mm/yy)

Principal/main diagnosis: _____

Secondary/other diagnosis: _____

Surgical operations/procedures: _____

_____

Any day case admissions?	NO ☐	YES ☐	NUMBER ☐☐
Any outpatient attendances?	NO ☐	YES ☐	NUMBER ☐☐
Any GP consultations?	NO ☐	YES ☐	NUMBER ☐☐
Any practice nurse consultations?	NO ☐	YES ☐	NUMBER ☐☐
Any community nurse visits?	NO ☐	YES ☐	NUMBER ☐☐

Analgesia Requirement

Please record the patients analgesia requirements over the previous 48 hours:

Drug	Total Dose

Additional information:

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
In-patient Information Form

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

In-patient Information Form

(To be completed by Research Nurse. Please complete text in BLOCK CAPITALS, tick the appropriate box or enter numbers into the boxes provided.)

Date of Admission: ☐☐/☐☐/☐☐ (dd/mm/yy)

Recruiting Consultant: _____

Patient's Date of Birth: ☐☐/☐☐/☐☐ (dd/mm/yy) Gender: MALE ☐ FEMALE ☐

Trial Leg: LEFT ☐ RIGHT ☐

SECTION 1: Admission and Discharge Details

Date of hospital admission: ☐☐/☐☐/☐☐

Date of Baseline Assessment: ☐☐/☐☐/☐☐

Date of angiogram: ☐☐/☐☐/☐☐

Date of randomisation: ☐☐/☐☐/☐☐

Date of primary intervention: ☐☐/☐☐/☐☐

Date of further intervention:- ☐☐/☐☐/☐☐

Date discharged from hospital: ☐☐/☐☐/☐☐

Date of death: ☐☐/☐☐/☐☐

Total number of days* in hospital: ☐☐.☐

Total number of days* in ITU: ☐☐.☐

Total number of days* in HDU: ☐☐.☐

(* - to nearest half day)

Status on discharge: Alive ☐ Dead ☐

Patient discharged to: Own home ☐
Other acute hospital ☐
Convalescent hospital ☐
Nursing home ☐
Other (specify) ☐ _____

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
In-patient Information Form

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

SECTION 2: Medication

a) Analgesia requirement 48 hours prior to intervention

Analgesia	Total Dose

b) Analgesia requirement 48 hours prior to discharge

Analgesia	Total Dose

c) Medication on discharge (only changes from admission drugs)

Drug name	Dose/unit	Frequency

SECTION 3: Other Tests

Date of Test	Type of Test	No. of Tests	Comments

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
In-patient Information Form

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

SECTION 3: Complications

(occurring during hospitalisation)

Complication		
New onset or worsening of angina	NO ☐	YES ☐
Myocardial infarction	NO ☐	YES ☐
TIA / amaurosis fugax	NO ☐	YES ☐
Stroke	NO ☐	YES ☐
Haematoma (no surgical drainage required)	NO ☐	YES ☐
Haematoma (surgical drainage required)	NO ☐	YES ☐
Wound infection (requiring antibiotics)	NO ☐	YES ☐
Chest infection (requiring antibiotics)	NO ☐	YES ☐
Urine infection (requiring antibiotics)	NO ☐	YES ☐
False aneurysm (not requiring surgical repair)	NO ☐	YES ☐
False aneurysm (requiring surgical repair)	NO ☐	YES ☐
Surgical intervention for other complication	NO ☐	YES ☐

Other (please specify):

Additional information:

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
In-patient Information Form

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

SECTION 4: Post-procedure clinical status

(to be completed at discharge or prior to secondary intervention, which ever is sooner).

Date of Assessment: ☐☐/☐☐/☐☐ (dd/mm/yy)

Brachial blood pressure: Right: ☐☐☐/☐☐☐ Left: ☐☐☐/☐☐☐

Ankle pressures in trial leg: *(insert not found* **[NF]** *if no signal insonated)*
for patients with compressible vessels record cuff pressure: for patients with incompressible ankle vessels record toe pressure or height (cm) above bed where Doppler signal lost (pole test)

	Cuff pressure	**or**	Height (cm) above bed	
Dorsalis pedis	☐☐☐ mmHg		☐☐☐ =	☐☐☐ mmHg
Posterior tibial	☐☐☐ mmHg		☐☐☐ =	☐☐☐ mmHg
Perforating peroneal	☐☐☐ mmHg		☐☐☐ =	☐☐☐ mmHg
Toe pressure	☐☐☐ mmHg			

Ankle:brachial pressure index in trial leg = ☐.☐☐
(highest ankle pressure/highest brachial pressure)

Rest Pain:	ABSENT	☐	IMPROVED	☐	UNCHANGED	☐
	WORSE	☐	NA	☐	AMPUTATION	☐
Ulceration:	HEALED	☐	IMPROVED	☐	NO CHANGE	☐
	WORSE	☐	NA	☐	AMPUTATION	☐
Gangrene:	ABSENT	☐	IMPROVED	☐	NO CHANGE	☐
	WORSE	☐	NA	☐	AMPUTATION	☐

(NA = Not Applicable)

Further intervention

Was there further intervention during this hospital admission NO ☐ YES ☐

If YES:

Date of Further Intervention: ☐☐/☐☐/☐☐ (dd/mm/yy)

Type: PTA ☐ SURGERY ☐ AMPUTATION ☐

Reason: COMPLICATION OF INTERVENTION ☐

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
In-patient Information Form

FAILURE OF INTERVENTION ☐ OTHER ☐

Timing: ELECTIVE ☐ EMERGENCY ☐

Please complete relevant Further Intervention Form

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Intervention Form (Surgery)

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

Intervention Form (Surgery)

(Please complete text in BLOCK CAPITALS, tick the appropriate box or enter numbers into the boxes provided. * - delete as necessary)

Date of Intervention: ☐☐/☐☐/☐☐ (dd/mm/yy)

Primary Intervention ☐ Further Intervention ☐

If Further Intervention: date of Primary Intervention ☐☐/☐☐/☐☐ (dd/mm/yy)

Recruiting Consultant Surgeon: _____

Patient's Date of Birth: ☐☐/☐☐/☐☐ (dd/mm/yy) Gender: MALE ☐ FEMALE ☐

Trial Leg: LEFT ☐ RIGHT ☐

SECTION 1: Surgery Details

(to be completed by the Consultant Surgeon please)

Time of arrival in anaesthetic room: ☐☐:☐☐ (hh:mm)

Time of start of anaesthetic procedures: ☐☐:☐☐ (hh:mm)

Time of start of operation: ☐☐:☐☐ (hh:mm)

Type of anaesthetic: GENERAL ☐ REGIONAL ☐

Type of graft:

Vein: LEG ☐ ARM ☐ COMPOSITE ☐
IN SITU ☐ REVERSED ☐

PTFE / Dacron*: Externally reinforced: NO ☐ YES ☐
+ Vein cuff / collar / boot* NO ☐ YES ☐

Other *(please specify)*: _____

Graft diameter: _____mm

Was systemic heparin administered?: NO ☐ YES ☐

Proximal anastomosis:		**Distal anastomosis:**	
Common femoral artery	☐	Above knee popliteal artery	☐
Deep femoral artery	☐	Below knee popliteal artery	☐
Superficial femoral artery	☐	Posterior tibial artery (upper / middle / lower* third)	☐
Above knee popliteal artery	☐	Anterior tibial artery (upper / middle / lower* third)	☐
Below knee popliteal artery	☐	Peroneal artery (upper / middle / lower* third)	☐
		Dorsalis pedis	☐

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Intervention Form (Surgery)

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

Immediate outcome (in the opinion of the senior surgeon present):

The graft was running satisfactorily at the end of the procedure: NO ☐ YES ☐

Was the operation combined with amputation:

NO ☐ DIGITS ☐ FOREFOOT ☐ TRANS-TIBIAL ☐ TRANS FEMORAL ☐

Time of departure from theatre: ☐☐:☐☐ (hh:mm)

Time of departure from recovery room: ☐☐:☐☐ (hh:mm)

Human Resources

(please enter numbers of each grade of staff present)

Surgeons:

Consultant	☐
Registrar	☐
Senior House Officer	☐
House Officer	☐

Anaesthetist:

Consultant	☐
Senior Registrar	☐
Registrar	☐
Senior House Officer	☐

Nursing Staff:

Grade A	☐	Grade B	☐
Grade C	☐	Grade D	☐
Grade E	☐	Grade F	☐
Grade G	☐		

Technicians:

ODA/ODP ☐

Additional information:

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Intervention Form (Surgery)

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

SECTION 2: Surgical Materials

(to be completed by theatre staff nurse; please enter the numbers of each item used during the procedure)

Sutures:

Prolene 6/0 W8597	☐☐
Prolene 6/0	☐☐
Vicryl 3/0 9717	☐☐
Vicryl 2/0 9150	☐☐
Vicryl 2/0 tie 9044	☐☐
CV6	☐☐
CV5	☐☐

Trays:

Medium Basic Trays	☐☐
Arterial Limbaneck	☐☐
Diathermy Tongs	☐☐
Diathermy Pad	☐☐
Diathermy Lead	☐☐
Vessel Retractor x2	☐☐
Embolectomy Catheter	☐☐
Needle holder	☐☐
Tunneling Tool	☐☐

Swabs and Gowns:

Gowns (disp) x 1	☐☐
Gowns (disp) x 3	☐☐
Gowns (linen) x 1	☐☐
Gowns (linen) x 3	☐☐
Swabs x 5 (Taped)	☐☐
Mepore Dressings	☐☐

Miscellaneous:

Suction Tubing	☐☐
Suction Catheters	☐☐
Opsite (Large)	☐☐
Irrigation Jet	☐☐
Discard-a-pad	☐☐
Masks	☐☐
Caps	☐☐
Sterile Gloves	☐☐

Additional Information / Equipment (excluding Scalpel Blades/Needles/Syringes and other items of nominal cost):

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Intervention Form (Surgery)

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

SECTION 3: Medications in Theatre

(to be completed by the anaesthetist please)

Regional Block:

Drug Name	Dose / % per ampoule	No of amps used
Bupivacaine	0.25%/10ml	
	0.50%/10ml	
	0.75%/10ml	
Other:		

Anaesthetic Drugs:

Drug Name	Dose / % per ampoule	No of amps used
Propofol	200 mg	
Propofol pre-filled syringes	500 mg	
Thiopentone	250 – 500 mg	
Fentanyl	100 µg	
Alfentanyl	1 mg	
Morphine	10 mg	
Diamorphine	10 mg	
Vecuronium	10 mg	
Atracurium	50 mg	
Methoxamine	20 mg	
Ephedrine	30 mg	
Heparin	5000 units	
Ondasetron	4 mg	
Neostigmine	2.5 mg	
Glycopyrrolate	600 µg	
Atropine	0.6 mg	
Midazolam	10 mg	
Water	10 ml	
Saline	10 ml	

Other Drugs:

Temazepam (pre-med)	10 mg	
Cefuroxime	750 mg	
Other:		

Maintenance Anaesthetic:

Isoflurane	
Sevoflurane	
Propofol	
Other:	

O_2	
N_2O	

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Intervention Form (Surgery)

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

SECTION 3: Medications in Theatre (cont.)

Intravenous Fluids:

Type	Volume of Units	Number Given
Hartmanns Solution	500 ml	
Normal Saline	500 ml	
Gelofusine	500 ml	
Other:		

Type	Volume of Units	Number Given
PPS	400 ml	
Dextran 70	500 ml	
Blood		

Equipment and Disposables Used by Anaesthetist:

Item	Number
IV Giving Sets	
IV Cannula: Venflon	
Arterial Cannula:	
Vygon Ledercath	
Arrow	
Vasocan	
Quickcath	
Arterial Pressure Kit	
Tegaderm Dressing	
Lectrocath	
CVP Catheter Set	
Regional Block Pack	
Regional Block Needle	
Stimuplex Needle	
3-way Tap	
Other:	

Item	Number
Endotracheal Tube	
Guedel Airway	
Post-op Oxygen Mask	
Nasal Cannulae	
Epidural Pack	
Spinal Needle: 22G	
Spinal Needle: 24G Sprottie	
Laryngeal Mask Airway	
"Bair Hugger" Warmine Blanket	
Syringes: 50 ml; 20 ml	
Syringes: 10 ml; 5 ml; 2 ml	
Needles	
ECG Electrodes	
Sterile Gloves	

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Intervention Form (PTA)

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

Intervention Form (PTA)

(Please complete text in BLOCK CAPITALS, tick the appropriate box or enter numbers into the boxes provided.)

Date of Intervention: ☐☐/☐☐/☐☐ (dd/mm/yy)

Primary Intervention ☐ Further Intervention ☐

If Further Intervention: date of Primary Intervention ☐☐/☐☐/☐☐ (dd/mm/yy)

Recruiting Consultant Radiologist: _____

Patient's Date of Birth: ☐☐/☐☐/☐☐ (dd/mm/yy) Gender: MALE ☐ FEMALE ☐

Trial Leg: LEFT ☐ RIGHT ☐

SECTION 1: PTA Details

(to be completed by the Consultant Radiologist please)

Time of arrival in angio-room: ☐☐:☐☐ (hh:mm)

Time of start of procedure: ☐☐:☐☐ (hh:mm)

PTA 1

Intention to treat: INTIMAL ☐ SUB-INTIMAL ☐

Treatment: INTIMAL ☐ SUB-INTIMAL ☐

Arterial segment treated:

- Superficial femoral artery ☐
- Above knee popliteal artery ☐
- Below knee popliteal artery ☐
- Posterior tibial artery ☐
- Anterior tibial artery ☐
- Peroneal artery ☐

Type of disease treated:

- Non-occlusive ☐
  - Focal stenosis ☐
  - Diffuse disease (<50% segment length) ☐
  - Diffuse disease (>50% segment length) ☐
- Occlusive ☐
  - Length of occlusion: _____ cm

Immediate outcome (in the opinion of the senior interventionalist):

- Complete technical success ☐
- Technical failure ☐
  - Failure to cross lesion ☐
  - Residual stenosis ☐
  - Distal embolism ☐
  - Other ☐

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Intervention Form (PTA)

Residual dissection ☐

PATIENT NUMBER ☐☐/☐☐☐☐☐/☐/☐

PTA 2

Intention to treat: INTIMAL ☐ SUB-INTIMAL ☐

Treatment: INTIMAL ☐ SUB-INTIMAL ☐

Arterial segment treated:

Superficial femoral artery ☐ Posterior tibial artery ☐
Above knee popliteal artery ☐ Anterior tibial artery ☐
Below knee popliteal artery ☐ Peroneal artery ☐

Type of disease treated:

Non-occlusive ☐ Occlusive ☐
Focal stenosis ☐ Length of occlusion: _____ cm
Diffuse disease (<50% segment length) ☐
Diffuse disease (>50% segment length) ☐

Immediate outcome (in the opinion of the senior interventionalist):

Complete technical success ☐
Technical failure ☐
Failure to cross lesion ☐ Distal embolism ☐
Residual stenosis ☐ Other ☐
Residual dissection ☐

PTA 3

Intention to treat: INTIMAL ☐ SUB-INTIMAL ☐

Treatment: INTIMAL ☐ SUB-INTIMAL ☐

Arterial segment treated:

Superficial femoral artery ☐ Posterior tibial artery ☐
Above knee popliteal artery ☐ Anterior tibial artery ☐
Below knee popliteal artery ☐ Peroneal artery ☐

Type of disease treated:

Non-occlusive ☐ Occlusive ☐
Focal stenosis ☐ Length of occlusion: _____ cm
Diffuse disease (<50% segment length) ☐ Segment occluded:
Diffuse disease (>50% segment length) ☐

Immediate outcome (in the opinion of the senior interventionalist):

Complete technical success ☐
Technical failure ☐
Failure to cross lesion ☐ Distal embolism ☐

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Intervention Form (PTA)

Residual stenosis ☐ Other ☐
Residual dissection ☐

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

Time of departure from angio-room: ☐☐:☐☐ (hh:mm)

Time of departure from recovery room: ☐☐:☐☐ (hh:mm)

Human Resources

(please enter numbers of each grade of staff present)

Radiologists:

Consultant ☐
Registrar ☐

Radiographers:

Superintendent ☐
Senior 1 ☐
Senior 2 ☐
Basic ☐

Nursing Staff:

Grade A ☐ Grade B ☐
Grade C ☐ Grade D ☐
Grade E ☐ Grade F ☐
Grade G ☐

Additional information:

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Intervention Form (PTA)

PATIENT NUMBER ☐☐/☐☐☐☐/☐☐

SECTION 2: Materials

(to be completed by staff nurse please)

Equipment:

	Number		Number
Disposable pack	☐☐	Needles	☐☐
Intensifier cover	☐☐	Syringes – 2, 5, 10ml	☐☐
Lead Screen cover	☐☐	Syringes – 20, 50ml	☐☐
One-way taps	☐☐	Luer lock syringe	☐☐
Puncture needles	☐☐		
Guidewires	☐☐	**Other (please specify):**	
Catheter	☐☐	_____	☐☐
Inflation device	☐☐	_____	☐☐
Balloon catheter – small vessel	☐☐	_____	☐☐
Balloon catheter – large vessel	☐☐	_____	☐☐
Sheath	☐☐	_____	☐☐
Perclose	☐☐		
Angioseal	☐☐		
Vasoseal	☐☐		

Medications and Fluids

Drug Name	Dose/ % per ampoule or Volume of Units	No of amps or units used
Heparin	1000 U/ml	
Lignocaine		
Betadine		
Contrast (please specify):		
NaCl	500 ml	
Hypnovel		
Other (please specify):		

Was a post-PTA angiogram performed? NO ☐ YES ☐

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Intervention Form (Amputation)

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

Intervention Form (Amputation)

(Please complete text in BLOCK CAPITALS, tick the appropriate box or enter numbers into the boxes provided.)

Date of Amputation: ☐☐/☐☐/☐☐ (dd/mm/yy)

Date of Previous Intervention: ☐☐/☐☐/☐☐ (dd/mm/yy)

Recruiting Consultant: _____

Patient's Date of Birth: ☐☐/☐☐/☐☐ (dd/mm/yy) Gender: MALE ☐ FEMALE ☐

Trial Leg: LEFT ☐ RIGHT ☐

Time of Last Follow-up: None ☐ 1/12 ☐ 3/12 ☐ 6/12 ☐

Date of Readmission: ☐☐/☐☐/☐☐ (dd/mm/yy)

SECTION 1: Amputation details

(to be completed by the Consultant Surgeon please)

Time of arrival in anaesthetic room: ☐☐:☐☐ (hh:mm)

Time of start of anaesthetic procedures: ☐☐:☐☐ (hh:mm)

Time of start of operation: ☐☐:☐☐ (hh:mm)

Type of anaesthetic: GENERAL ☐ REGIONAL ☐

Leg amputated: LEFT ☐ RIGHT ☐

Level of amputation: DIGITS ☐ FOREFOOT ☐

TRANS-TIBIAL ☐ TRANS-FEMORAL ☐

Time of departure from theatre: ☐☐:☐☐ (hh:mm)

Time of departure from recovery room: ☐☐:☐☐ (hh:mm)

Amputation at the trans-tibial or trans-femoral level constitute a primary end-point of the trial and further follow-up is no longer required.

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Intervention Form (Amputation)

Patients undergoing amputation of the digits or forefoot remain as trial participants and continue being followed-up.

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

Human Resources

(please enter numbers of each grade of staff present)

Surgeons:

Consultant	☐
Registrar	☐
Senior House Officer	☐
House Officer	☐

Anaesthetist:

Consultant	☐
Senior Registrar	☐
Registrar	☐
Senior House Officer	☐

Nursing Staff:

Grade A	☐	Grade B	☐
Grade C	☐	Grade D	☐
Grade E	☐	Grade F	☐
Grade G	☐		

Technicians:

ODA/ODP ☐

Additional information:

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Intervention Form (Amputation)

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

SECTION 2: Surgical Materials

(to be completed by theatre staff nurse; please enter the numbers of each item used during the procedure)

Sutures:

Prolene 3/0	☐☐
Prolene 2/0	☐☐
Vicryl 1/0 ties	☐☐
Vicryl 2/0 tie 9044	☐☐
Silk 2/0	☐☐
Other	☐☐

Trays:

Medium Basic Trays	☐☐
Amputation	☐☐
Diathermy Tongs	☐☐
Diathermy Pad	☐☐
Diathermy Lead	☐☐
Diathermy Tip	☐☐

Swabs and Gowns:

Gowns (disp) x 1	☐☐
Gowns (disp) x 3	☐☐
Gowns (linen) x 1	☐☐
Gowns (linen) x 3	☐☐
Swabs x 5 (Taped)	☐☐
Swabs x 5 (10 x 10)	☐☐

Miscellaneous:

Redivac Drain	☐☐
Discard-a-pad	☐☐
Masks	☐☐
Caps	☐☐
Sterile Gloves	☐☐

Dressing (please specify type): _____

Additional Information / Equipment (excluding Scalpel Blades and other items of nominal cost):

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Intervention Form (Amputation)

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

SECTION 3: Medications in Theatre

(to be completed by the anaesthetist please)

Regional Block:

Drug Name	Dose / % per ampoule	No of amps used
Bupivacaine	0.25%/10ml	
	0.50%/10ml	
	0.75%/10ml	
Other:		

Anaesthetic Drugs:

Drug Name	Dose / % per ampoule	No of amps used
Propofol	200 mg	
Propofol pre-filled syringes	500 mg	
Thiopentone	250 – 500 mg	
Fentanyl	100 µg	
Alfentanyl	1 mg	
Morphine	10 mg	
Diamorphine	10 mg	
Vecuronium	10 mg	
Atracurium	50 mg	
Methoxamine	20 mg	
Ephedrine	30 mg	
Heparin	5000 units	
Ondasetron	4 mg	
Neostigmine	2.5 mg	
Glycopyrrolate	600 µg	
Atropine	0.6 mg	
Midazolam	10 mg	
Water	10 ml	
Saline	10 ml	

Other Drugs:

Temazepam (pre-med)	10 mg	
Cefuroxime	750 mg	
Other:		

Maintenance Anaesthetic:

Isoflurane	
Sevoflurane	
Propofol	
Other:	

O_2	
N_2O	

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
Intervention Form (Amputation)

PATIENT NUMBER ☐☐/☐☐☐☐/☐/☐

SECTION 3: Medications in Theatre (cont.)

Intravenous Fluids:

Type	Volume of Units	Number Given
Hartmanns Solution	500 ml	
Normal Saline	500 ml	
Gelofusine	500 ml	
Other:		

Type	Volume of Units	Number Given
PPS	400 ml	
Dextran 70	500 ml	
Blood		

Equipment and Disposables Used by Anaesthetist:

Item	Number
IV Giving Sets	
IV Cannula: Venflon	
Arterial Cannula:	
Vygon Ledercath	
Arrow	
Vasocan	
Quickcath	
Arterial Pressure Kit	
Tegaderm Dressing	
Lectrocath	
CVP Catheter Set	
Regional Block Pack	
Regional Block Needle	
Stimuplex Needle	
3-way Tap	
Other:	

Item	Number
Endotracheal Tube	
Guedel Airway	
Post-op Oxygen Mask	
Nasal Cannulae	
Epidural Pack	
Spinal Needle: 22G	
Spinal Needle: 24G Sprottie	
Laryngeal Mask Airway	
"Bair Hugger" Warmine Blanket	
Syringes: 50 ml; 20 ml	
Syringes: 10 ml; 5 ml; 2 ml	
Needles	
ECG Electrodes	
Sterile Gloves	

Appendix 4

Health-related quality of life forms

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
VascuQol Form

PATIENT NUMBER ☐☐/☐☐☐☐/☐☐

VascuQol Questionnaire

(To be completed by the patient at follow-up. Please complete text in BLOCK CAPITALS, tick the appropriate box.)

Date of Completion: ☐☐/☐☐/☐☐ (dd/mm/yy)

Full Name: _____

Date of Birth: ☐☐/☐☐/☐☐ (dd/mm/yy)

Hospital Name: _____

Completed at: 3 months ☐ 6 months ☐ 12 months ☐
2 years ☐ 3 years ☐ 4 years ☐

Instructions: These questions ask you how you have been affected by poor circulation to your legs over the last two weeks.
You will be asked about the symptoms you have had, the way that your activities have been affected and how you have been feeling.
Please read each bit of the answer and then tick the one that applies best to you.
If you are unsure about how to answer a question, please give the best answer you can.
There is no right or wrong answer.
Please answer every question. Thank you.

1. In the last two weeks **I have had pain in the leg (or foot) when walking** ……

(tick one)

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

2. In the last two weeks **I have been worried that I might injure my leg** ……

(tick one)

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
VascuQol Form

3. In the last two weeks **cold feet have given me** …….

(tick one)

1. A very great deal of discomfort or distress ☐ 1
2. A great deal of discomfort or distress ☐ 2
3. A good deal of discomfort or distress ☐ 3
4. A moderate amount of discomfort or distress ☐ 4
5. Some discomfort or distress ☐ 5
6. Very little discomfort or distress ☐ 6
7. No discomfort or distress ☐ 7

4. In the last two weeks, because of the poor circulation to my legs, **my ability to take exercise or to play any sports has been** …..

(tick one)

1. Totally limited, couldn't exercise at all ☐ 1
2. Extremely limited ☐ 2
3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

5. In the last two weeks **my legs have felt tired or weak** …..

(tick one)

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

6. In the last two weeks, because of the poor circulation to my legs, **I have been restricted in spending time with my friends or relatives** …..

(tick one)

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
VascuQol Form

7. In the last two weeks **I have had pain in the foot (or leg) after going to bed at night** ….

(tick one)

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

8. In the last two weeks **pins and needles or numbness in my leg (or foot)** have caused me ….

(tick one)

1. A very great deal of discomfort or distress ☐ 1
2. A great deal of discomfort or distress ☐ 2
3. A good deal of discomfort or distress ☐ 3
4. A moderate amount of discomfort or distress ☐ 4
5. Some discomfort or distress ☐ 5
6. Very little discomfort or distress ☐ 6
7. No discomfort or distress ☐ 7

9. In the last two weeks **the distance I can <u>walk has improved</u>** ….

(tick one)

1. Not at all (tick this if distance is unchanged or has decreased) ☐ 1
2. A little ☐ 2
3. Somewhat ☐ 3
4. Moderately ☐ 4
5. A good deal ☐ 5
6. A great deal ☐ 6
7. A very great deal ☐ 7

10. In the last two weeks, because of the poor circulation to my legs, **my ability to walk has been**

(tick one)

1. Totally limited, couldn't walk at all ☐ 1
2. Extremely limited ☐ 2
3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
VascuQol Form

11. In the last two weeks **being (or becoming) housebound has been a concern of mine** .....

(tick one)

1. A very great deal ☐ 1
2. A great deal ☐ 2
3. A good deal ☐ 3
4. Moderately ☐ 4
5. Somewhat ☐ 5
6. A little ☐ 6
7. Not at all ☐ 7

12. In the last two weeks **I have been concerned about having poor circulation to my legs** .....

(tick one)

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

13. In the last two weeks **I have had pain in the foot (or leg) when I am at rest** .....

(tick one)

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

14. In the last two weeks, because of the poor circulation to my legs, **my ability to climb stairs has been** .....

(tick one)

1. Totally limited, couldn't climb stairs at all ☐ 1
2. Extremely limited ☐ 2
3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
VascuQol Form

15. In the last two weeks, because of the poor circulation to my legs, **my ability to take part in social activities has been** …..

(tick one)

1. Totally limited, couldn't socialise at all ☐ 1
2. Extremely limited ☐ 2
3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

16. In the last two weeks, because of the poor circulation to my legs, **my ability to perform routine household work has been** …..

(tick one)

1. Totally limited, couldn't perform housework at all ☐ 1
2. Extremely limited ☐ 2
3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

17. In the last two weeks **ulcers in the leg (or foot) have given me pain or distress** …..

(tick one)

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time (tick this if you do not have leg ulcers) ☐ 7

18. Because of poor circulation to my legs, **the overall range of activities that I would have liked to do in the last two weeks has been** …..

(tick one)

1. Severely limited – most activities not done ☐ 1
2. Very limited ☐ 2
3. Moderately limited – several activities not done ☐ 3
4. Slightly limited ☐ 4
5. Very slightly limited – very few activities not done ☐ 5
6. Hardly limited at all ☐ 6
7. Not limited at all – have done all the activities that I wanted to ☐ 7

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
VascuQol Form

19. In the last two weeks **the poor circulation to the legs have made me feel frustrated** …..

(tick one)

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

20. In the last two weeks **when I do get pain in my leg (or foot) it has given me** ….

(tick one)

1. A very great deal of discomfort or distress ☐ 1
2. A great deal of discomfort or distress ☐ 2
3. A good deal of discomfort or distress ☐ 3
4. A moderate amount of discomfort or distress ☐ 4
5. Some discomfort or distress ☐ 5
6. Very little discomfort or distress ☐ 6
7. No discomfort or distress ☐ 7

21. In the last two weeks **I have felt guilty about relying on friends or relatives** …..

(tick one)

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

22. In the last two weeks, because of the poor circulation to my legs, **my ability to go shopping or carry bags has been** …..

(tick one)

1. Totally limited, couldn't go shopping at all ☐ 1
2. Extremely limited ☐ 2
3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
VascuQol Form

23. In the last two weeks **I have worried I might be in danger of losing a part of my leg or foot**

(tick one)

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

24. In the last two weeks **the distance I can walk <u>has become less</u>** .....

1. A very great deal ☐ 1
2. A great deal ☐ 2
3. A good deal ☐ 3
4. Moderately ☐ 4
5. Somewhat ☐ 5
6. A little ☐ 6
7. Not at all – tick if distance is unchanged or has increased ☐ 7

25. In the last two weeks **I have been depressed about the poor circulation to my legs** .....

(tick one)

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

Thank you for completing this questionnaire

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
SF-36 Form

PATIENT NUMBER ☐☐/☐☐☐☐/☐☐

SF-36 Health Survey

(To be completed by the patient at follow-up. Please complete text in BLOCK CAPITALS, tick the appropriate box or circle the relevant number.)

Date of Completion: ☐☐/☐☐/☐☐ (dd/mm/yy)

Full Name: _____

Date of Birth: ☐☐/☐☐/☐☐ (dd/mm/yy)

Hospital Name: _____

Completed at: 3 months ☐ 6 months ☐ 12 months ☐
2 years ☐ 3 years ☐ 4 years ☐

Instructions: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

	(tick one)
Excellent	☐ 1
Very good	☐ 2
Good	☐ 3
Fair	☐ 4
Poor	☐ 5

2. Compared to one year ago, how would you rate your health in general now?

	(tick one)
Much better than than one year ago	☐ 1
Somewhat better than one year ago	☐ 2
About the same as one year ago	☐ 3
Somewhat worse than one year ago	☐ 4
Much worse than one year ago	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

Activity	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	1	2	3
c) Lifting or carrying groceries	1	2	3
d) Climbing **several** flights of stairs	1	2	3
e) Climbing **one** flight of stairs	1	2	3
f) Bending, kneeling or stooping	1	2	3
g) Walking **more than a mile**	1	2	3
h) Walking **half a mile**	1	2	3
i) Walking **one hundred yards**	1	2	3
j) Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(circle one number on each line)

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities	1	2
b) **Accomplished less** than you would like	1	2
c) Were limited in the **kind** of work or other activities	1	2
d) Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
SF-36 Form

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities	1	2
b) **Accomplished less** than you would like	1	2
c) Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interferred with your normal social activities with family, friends, neighbours or groups?

(tick one)

- Not at all ☐ 1
- Slightly ☐ 2
- Moderately ☐ 3
- Quite a bit ☐ 4
- Extremely ☐ 5

7. How much bodily pain have you had during the past 4 weeks?

(tick one)

- None ☐ 1
- Very mild ☐ 2
- Mild ☐ 3
- Moderate ☐ 4
- Severe ☐ 5
- Very severe ☐ 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(tick one)

- Not at all ☐ 1
- A little bit ☐ 2
- Moderately ☐ 3
- Quite a bit ☐ 4
- Extremely ☐ 5

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
SF-36 Form

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

(circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a) Did you feel full of life?	1	2	3	4	5	6
b) Have you been a very nervous person?	1	2	3	4	5	6
c) Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d) Have you felt calm and peaceful?	1	2	3	4	5	6
e) Did you have a lot of energy?	1	2	3	4	5	6
f) Have you felt downhearted and low?	1	2	3	4	5	6
g) Did you feel worn out?	1	2	3	4	5	6
h) Have you been a happy person?	1	2	3	4	5	6
i) Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.)?

(tick one)

- All of the time ☐ 1
- Most of the time ☐ 2
- Some of the time ☐ 3
- A little of the time ☐ 4
- None of the time ☐ 5

11. How TRUE or FALSE is each of the following statements for you?

(circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a) I seem to get ill a little easier than other people	1	2	3	4	5
b) I am as healthy as anybody I know	1	2	3	4	5
c) I expect my health to get worse	1	2	3	4	5
d) My health is excellent	1	2	3	4	5

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
EuroQol (EQ-5D) questionnaire

Case Reference No._____

Baseline EuroQol Questionnaire

(To be completed by the patient prior to randomisation. Please complete text in BLOCK CAPITALS, tick the appropriate box or enter numbers into the boxes provided.)

Date of Completion: ☐☐/☐☐/☐☐ (dd/mm/yy)

Full Name: _____

Date of Birth: ☐☐/☐☐/☐☐ (dd/mm/yy)

Hospital Name: _____

Instructions: Please tick one alternative of each group below to show which statement best describes your health today. Do not tick more than one box in each group.

Mobility

- I have no problems in walking about ☐ 1
- I have some problems in walking about ☐ 2
- I am confined to bed ☐ 3

Self Care

- I have no problems with self care ☐ 1
- I have some problems washing and dressing myself ☐ 2
- I am unable to wash or dress myself ☐ 3

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems performing my usual activities ☐ 1
- I have some problems performing my usual activities ☐ 2
- I am unable to perform my usual activities ☐ 3

Pain/Discomfort

- I have no pain or discomfort ☐ 1
- I have moderate pain or discomfort ☐ 2
- I have extreme pain or discomfort ☐ 3

Anxiety/Depression

- I am not anxious or depressed ☐ 1
- I am moderately anxious or depressed ☐ 2
- I am extremely anxious or depressed ☐ 3

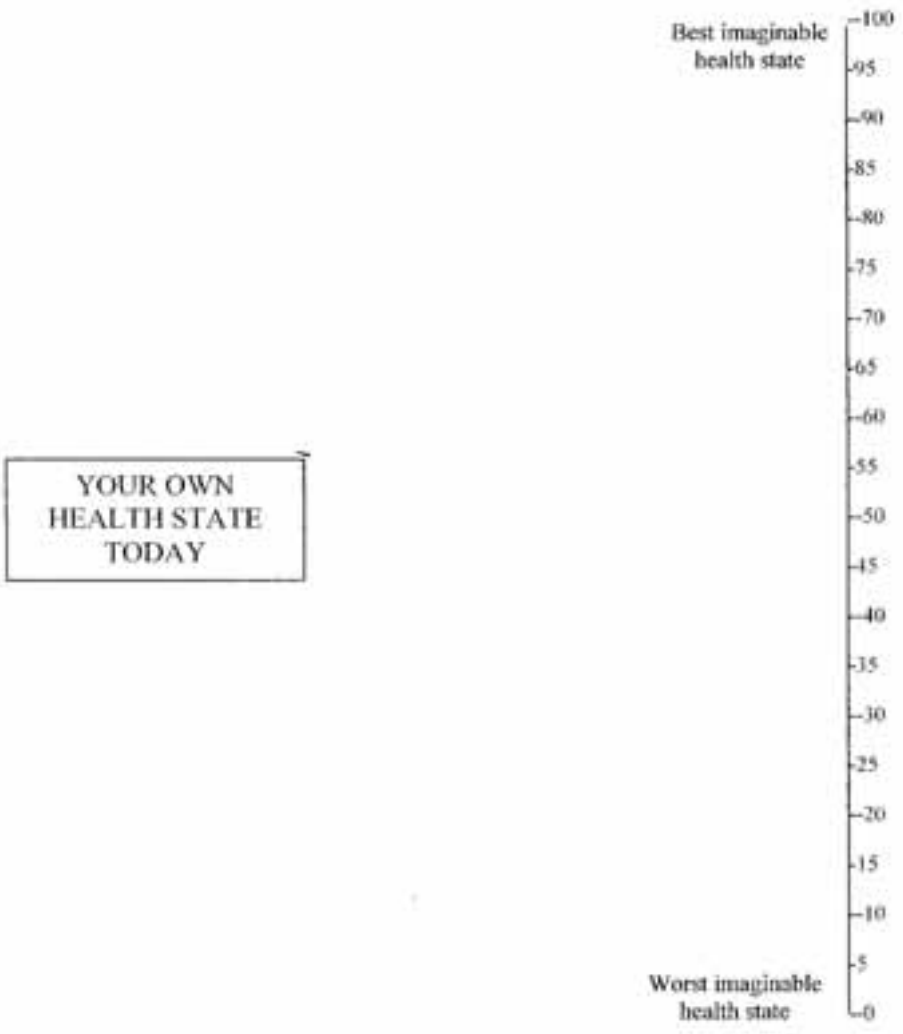
Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
EuroQol (EQ-5D) questionnaire

Case Reference No._____

EuroQol Valuation Question

To help people say how good or bad a health status is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point of the scale indicates how good or bad your current health state is.



Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
EuroQol (EQ-5D) questionnaire

PATIENT NUMBER ☐☐/☐☐☐☐/☐☐

EuroQol Questionnaire

(To be completed by the patient at follow-up. Please complete text in BLOCK CAPITALS, tick the appropriate box or enter numbers into the boxes provided.)

Date of Completion: ☐☐/☐☐/☐☐ (dd/mm/yy)

Full Name: _____

Date of Birth: ☐☐/☐☐/☐☐ (dd/mm/yy)

Hospital Name: _____

Completed at: 3 months ☐ 6 months ☐ 12 months ☐
2 years ☐ 3 years ☐ 4 years ☐

Instructions: Please tick one alternative of each group below to show which statement best describes your health today. Do not tick more than one box in each group.

Mobility

- I have no problems in walking about ☐ 1
- I have some problems in walking about ☐ 2
- I am confined to bed ☐ 3

Self Care

- I have no problems with self care ☐ 1
- I have some problems washing and dressing myself ☐ 2
- I an unable to wash or dress myself ☐ 3

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- I have extreme pain or discomfort ☐ 3

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- I am not anxious or depressed ☐ 1
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- I am extremely anxious or depressed ☐ 3

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial
EuroQol (EQ-5D) questionnaire

PATIENT NUMBER ☐☐/☐☐☐☐/☐☐

EuroQol Valuation Question

To help people say how good or bad a health status is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

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We look forward to hearing from you.

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