Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy

Andrew W. Bradbury, BSc, MD, MBA, FRCSEd,[a,b] Donald J. Adam, MD, FRCSEd,[a] Jocelyn Bell, PhD,[b] John F. Forbes, PhD,[c] F. Gerry R. Fowkes, PhD, FRCPE,[d] Ian Gillespie, MD, FRCR,[e] Charles Vaughan Ruckley, ChM, FRCSEd, CBE,[f] and **Gillian M. Raab, PhD,[g] on behalf of the BASIL trial Participants,*** *Birmingham and Edinburgh, United Kingdom*

Background: **A 2005 interim analysis of the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial showed that in patients with severe lower limb ischemia (SLI; rest pain, ulceration, gangrene) due to infrainguinal disease, bypass surgery (BSX)-first and balloon angioplasty (BAP)-first revascularization strategies led to similar short-term clinical outcomes, although BSX was about one-third more expensive and morbidity was higher. We have monitored patients for a further 2.5 years and now report a final intention-to-treat (ITT) analysis of amputation-free survival (AFS) and overall survival (OS).**
Methods: **Of 452 enrolled patients in 27 United Kingdom hospitals, 228 were randomized to a BSX-first and 224 to a BAP-first revascularization strategy. All patients were monitored for 3 years and more than half for >5 years.**
Results: **At the end of follow-up, 250 patients were dead (56%), 168 (38%) were alive without amputation, and 30 (7%) were alive with amputation. Four were lost to follow-up. AFS and OS did not differ between randomized treatments during the follow-up. For those patients surviving 2 years from randomization, however, BSX-first revascularization was associated with a reduced hazard ratio (HR) for subsequent AFS of 0.85 (95% confidence interval [CI], 0.5-1.07; $P = .108$) and for subsequent OS of 0.61 (95% CI, 0.50-0.75; $P = .009$) in an adjusted, time-dependent Cox proportional hazards model. For those patients who survived for 2 years after randomization, initial randomization to a BSX-first revascularization strategy was associated with an increase in subsequent restricted mean overall survival of 7.3 months (95% CI, 1.2-13.4 months, $P = .02$) and an increase in restricted mean AFS of 5.9 months (95% CI, 0.2-12.0 months, $P = .06$) during the subsequent mean follow-up of 3.1 years (range, 1-5.7 years).**
Conclusions: **Overall, there was no significant difference in AFS or OS between the two strategies. However, for those patients who survived for at least 2 years after randomization, a BSX-first revascularization strategy was associated with a significant increase in subsequent OS and a trend towards improved AFS. (J Vasc Surg 2010;51:5S-17S.)**

Severe leg ischemia (SLI), characterized 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.[1] Many observational data examining outcomes after surgical and endovascular interventions have been published from many different countries around the world[2-28] and many opinions expressed about the relative merits of these two approaches to revascularization.[29-32] Despite this, the absence of level I evidence from randomized trials (RCTs) means that there is continuing debate and disagreement on how such patients are best treated.[33,34]

The United Kingdom (UK)-based, multicenter Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial was funded by the UK National Institute of Health Research (NIHR) Health Technology Assessment (HTA) program (http://www.hta.ac.uk/) in 1998 and remains the only RCT to compare the clinical and cost-effectiveness of a bypass surgery (BSX)-first and a balloon angioplasty

From Vascular Surgery, University of Birmingham and Vascular and Endovascular Surgery, Heart of England NHS Foundation Trust,[a] University of Birmingham,[b] Birmingham; Health Economics,[c] and Epidemiology[d] University of Edinburgh, Edinburgh; Interventional Radiology, Edinburgh; Royal Infirmary and University of Edinburgh[e]; Vascular Surgery, University of Edinburgh[f]; and School of Nursing, Midwifery and Social Care, Edinburgh Napier University, Edinburgh.[g]

*The BASIL trial participants are listed in the Appendix.

Support: The BASIL trial was funded by the UK National Health Service (NHS) Research and Development Health Technology Assessment (HTA) Programme. The views and opinions expressed here are not necessarily those of the UK NHS or HTA.

Competition of interest: The authors have had full access to the data and take responsibility for its integrity; read and agree to the manuscript as written; and have no conflict of interest to declare.

Correspondence: Professor Andrew W. Bradbury, Principal Investigator, Department of Vascular Surgery, University of Birmingham, Heart of England NHS Foundation Trust, Netherwood House, Solihull Hospital, Lode Lane, Birmingham, B91 2JL, UK (e-mail: Andrew.Bradbury@btinternet.com).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

0741-5214/$36.00

doi:10.1016/j.jvs.2010.01.073

(BAP)-first revascularization strategy for SLI due to infrainguinal disease.[35]

The term severe leg ischemia (SLI), rather than critical limb ischemia (CLI), was intentionally used when the trial was designed in the late 1990s because trial organizers wished specifically to admit patients with chronic, potentially limb threatening, ischemia but who did not necessarily have ankle pressures <50 mm Hg and thus did not strictly fulfill the requirements of the term CLI as defined by the European Consensus Document.[36] It is also important to emphasize at the outset that BASIL was not a trial of all patients presenting with SLI due to infrainguinal disease. Rather, BASIL only considers those who required and were fit for immediate or early revascularization and in whom there was uncertainty (gray area of clinical equipoise) about which treatment strategy (BSX first or BAP first) was preferable in the judgement of the responsible surgical and interventional teams. Lastly, it is important to bear in mind that the BASIL trial compares two strategies, not just procedures, and the outcomes reported here therefore take into account events occurring both before and after the index procedure.[37]

An interim intention-to-treat (ITT) analysis reported in 2005 indicated that short-term amputation free survival (AFS) and overall survival (OS) were similar after the two strategies, but BSX was more morbid during the first 12 months and approximately one-third more expensive.[35] However, there was a suggestion that after 2 years from randomization, patients would be more likely to remain alive and without amputation if they had been originally randomized to BSX. Although this result was statistically significant, it was based on a post hoc analysis performed after the survival curves had been viewed, and the number of end points after 2 years was relatively small. To determine whether this apparent advantage of BSX was maintained in the longer term, patients have now been monitored for a further 2.5 years. We now report a final ITT analysis of AFS and OS in patients randomized to a BSX-first or a BAP-first revascularization strategy for SLI due to infra-inguinal disease.

METHODS

All patients who participated in BASIL provided written informed consent. The study was approved by the Multi-centre Research Ethics Committee (MREC) for Scotland. The BASIL trial is registered with the National Research Register (NRR) and as an International Standard Randomised Controlled Trial, number ISRCTN 45398889 (http://www.controlled-trials.com/ISRCTN45398889/45398889 17-05-2009).

Design. The BASIL trial methods have been published in detail elsewhere.[35] Briefly, between August 1999 and June 2004, consultant vascular surgeons and interventional radiologists in 27 UK hospitals randomized 452 patients with SLI to a BSX-first or a BAP-first treatment strategy whose diagnostic imaging showed a pattern of disease which, in their joint opinion, could equally well be treated by infrainguinal BSX or BAP. SLI was defined as ischemic rest and/or night pain (requiring opiate analgesia) and/or tissue loss (ulcer and/or gangrene) of presumed arterial etiology (regardless of ankle pressure) present for >2 weeks. It is important to emphasize that a patient could only be randomized if there was genuine doubt on the part of the responsible vascular team about which strategy was in the patient's best interests, and if the patient required, agreed to, and was fit for urgent or immediate revascularization by either means.

After patients were randomized by center, patients in each center were then further stratified into four groups by clinical presentation (rest pain only vs tissue loss) and ankle pressure (≥50 vs <50 mm Hg). Preintervention angiograms were scored according to the Bollinger method.[38,39]

Centers were encouraged to undertake the assigned procedure as soon as possible after patient randomization. Responsible consultant vascular surgeons and interventionalists were permitted to use their normal custom and practice with regard to preintervention assessment, the intervention itself, and postintervention follow-up.

Data on all first and repeat interventions were prospectively collected, as were data on clinical outcomes. For the first year of follow-up, four dedicated research nurses travelled regularly to trial centers to collect data on randomized patients. Thereafter, the local vascular teams collected the data. The trial coordinator liaised continually with these teams and travelled at least annually to trial centers to collect data from paper-based and electronic hospital information systems regarding further procedures and primary outcomes. Where necessary, primary care doctors and nurses were also contacted.

In addition, end point data for deaths, amputations, and further procedures were collected through national audit mechanisms. Specifically, details of patients recruited in Scottish centers were logged with the Information and Statistics Division (ISD) of the National Health Service in Scotland. The status of all patients alive at the end of follow-up was confirmed by linkage to the General Registry Office (Scotland) or the Office of National Statistics (ONS) England death records. Hospital admissions for Scottish patients were obtained by record linkage to Scottish Morbidity Records (SMR-01).

Final follow-up data were gathered from visits to all centers in the 6 months before the end of follow-up. These data were checked and updated to the final follow-up date using data from UK National Health Service (NHS) sources, including the ISD of the NHS in Scotland using record linkage to SMR-01 records, General Registry Office (Scotland), and the ONS England death records, hospital records, and general practitioners.

In keeping with the 2005 interim analysis,[35] the main clinical end points reported here are AFS, defined as patient alive without amputation of trial leg at transtibial level or above, and OS, defined as death from any cause. Secondary outcomes included postprocedural morbidity, reinterventions, health-related quality of life (HRQOL), and the use of hospital resources. Analyses of these secondary clinical

outcomes and a detailed HRQOL and cost-effectiveness analysis are the subject of further separate reports.[37,40]

Statistical analysis. The power to detect a hazard ratio (HR) of 0.5 for BSX vs BAP from new events (amputation, death) after 2 years from randomization was estimated at 90% with $P = .05$. This was based on a simulation study using a Weibull parametric survival model using separate hazards before and after 2 years from randomization. Because the expected direction of difference was known, a one-sided test was specified and agreed by the funding body (HTA) and data monitoring committee. This present, second statistical analysis was conducted according to a prespecified protocol that was finalized before further follow-up data from 2005 to 2008 were available. In keeping with accepted reporting standards for RCTs, all analyses presented here are by ITT. A by-treatment-received analysis of AFS and OS is the subject of a separate report.[37]

A Cox proportional hazards model was used to examine AFS and OS with a time-dependent HR to compare treatments taking different values before and after 2 years from randomization. For the survival analyses, patients with no report of death were censored at the date of last clinical contact or at the date of the last record linkage to NHS data (end February 2007 for ISD and end July 2007 for ONS). 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; these were all within 1 year and 1 month of randomization.

RESULTS

The baseline characteristics of the 228 patients randomized to BSX and the 224 randomized to BAP were similar and have been previously reported in detail, as have the details of the BSX and BAP procedures performed.[35] As is typical of patients presenting with SLI, many were elderly, >40% were diabetic, >33% were still smoking, most had a significant cardiovascular medical history, and the SLI in 25% affected both legs. Disease severity in the trial leg was rest pain only and an ankle pressure ≥50 mm Hg in 93; rest pain only and an ankle pressure <50 mm Hg in 23; tissue loss and an ankle pressure ≥50 mm Hg in 222, and tissue loss and an ankle pressure <50 mm Hg in 114. Thus, 74% of patients had tissue loss (ulceration, gangrene) and 30% had ankle pressures <50 mm Hg, thus fulfilling the European Consensus pressure criteria for CLI.[36]

Apart from four patients lost to follow-up, there was a minimum of 3 years complete follow-up for all patients, with 54% being monitored for >5 years; the longest follow-up was just >7 years. The status of the patients at the end of follow-up is reported in Table I. Procedures undertaken out to 3 years are shown in the Consolidated Standards of Reporting Trials (CONSORT) diagram (Fig 1).

For follow-up period as a whole, restricted mean survival[41] did not differ significantly between randomized groups for AFS, with 3.84 years for BSX and 3.62 years for BAP (difference, 0.22 years; 95% confidence interval [95% CI], −0.34 to 0.78) or OS, with 4.48 years for BSX and 4.25 years for BAP (difference, 0.23 years; 95% CI, −0.33 to 0.79). However, as had been anticipated from the interim analysis,[35] the time-dependent Cox proportional hazards analysis prespecified in the statistical plan showed the relative HRs for amputation and death after BSX and BAP were more favorable for BSX at later times. Specifically, whereas hazards were slightly (nonsignificantly) higher for BSX out to 2 years from randomization, OS was significantly better after 2 years in those patients initially randomized to BSX (Table II). Although there was also a trend towards better AFS in the BSX group after 2 years, this was not statistically significant. These findings are shown in the survival curves in Figs 2 and 3.

Table I. Patient status at final follow-up

Variable	*All (n = 452) No. (%)*	*Angioplasty (n = 224) No. (%)*	*Bypass (n = 228) No. (%)*
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)

For those patients who survived to 2 years after randomization, initial randomization to BSX was associated with a significant increase in subsequent restricted mean OS of 7.3 months ($P = .02$) and a nonsignificant increase in restricted mean AFS of 5.9 months ($P = .06$) during a subsequent mean follow-up of 3.1 years (range, 1-5.7 years) compared with randomization to BAP.

To explore further information coming from new data collected since the interim census date (February 2005), we also performed a person-years analysis of events that occurred after 2 years from randomization. This showed that the trend to improved AFS after 2 years seen after randomization to BSX in the earlier preliminary (2005) analysis was not continued. This was because relatively more amputations occurred after 2 years in those who had been assigned to BSX. By contrast, the trend to significantly fewer deaths in those randomized to BSX did continue. These data are in agreement with and support the results of the prespecified Cox proportional hazards analysis.

There was no evidence for differential effectiveness by any of the interactions prespecified in the statistical protocol; namely, Bollinger angiography scores, Trans-Atlantic Inter-Society Consensus (TASC) II classification, stratification group at randomization, 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 and when the periods before and after 2 years from randomization were analyzed separately. No other interactions, outside of those prespecified, were examined.

DISCUSSION

Background to the current analysis. The UK National Institute of Health Research (NIHR) Health Tech-

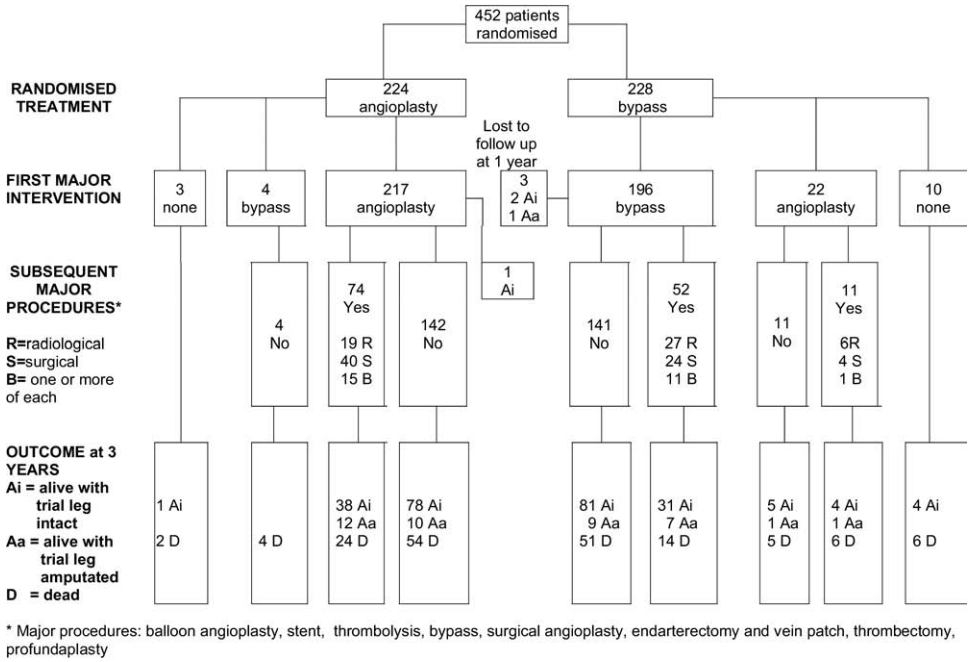

Fig 1. Consolidated Standards of Reporting Trials (CONSORT) diagram shows patient journeys and interventions out to 3 years.

Table II. Cox proportional hazards analysis, by time from randomization <2 years and >2 years

End point	*Time from randomization*	*HR surgery vs angioplasty*			*Treatment by time period* P *value*[a]
		Estimate	*95% CI*	P *value*	
Amputation free survival					
Unadjusted	<2 years	1.05	(0.78-1.41)	0.76	.26
	>2 years	0.80	(0.55-1.16)	0.24	
Adjusted[b]	<2 years	1.03	(0.76-1.39)	0.85	.23
	>2 years	0.85	(0.50-1.07)	0.11	
Overall survival					
Unadjusted	<2 years	1.17	(0.83-1.65)	0.36	.013
	>2 years	0.62	(0.43-0.90)	0.01	
Adjusted[b]	<2 years	1.19	(0.84-1.68)	0.32	.011
	>2 years	0.61	(0.50-0.75)	0.009	

CI, Confidence interval; *HR,* hazard ratio.
[a]Test of homogeneity of HR before and after 2 years from randomization.
[b]Adjusted for stratification, serum creatinine, body mass index, diabetes, age, smoking, statin at baseline, and below knee Bollinger score.

nology Assessment (HTA) program (http://www.hta.ac.uk/) invited tenders for a trial to compare surgical and endovascular approaches to the treatment of lower limb-threatening ischemia in 1996, and our group was chosen to 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 >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 since then have exhibited one or more of the methodologic limitations that originally prompted the commissioning of the BASIL trial in the late 1990s. Specifically, these other studies were often retrospective,[42-44] from a single-center,[42,45,46] were single-surgeon, small,[47,48] had mixed patients with claudication and SLI,[46,47,49] had mixed aortoiliac and infrainguinal disease,[45] provided only short[15,47,49] and/or incomplete[44] follow-up, excluded technical failures,[50] and used nonclinical surrogate end points.[51]

Despite these methodologic problems, the paucity of good quality data, and concerns over durability,[52] especially in patients with more advanced disease,[53] certain review articles continue to strongly advocate an endovascular rather than a surgical approach to SLI as the

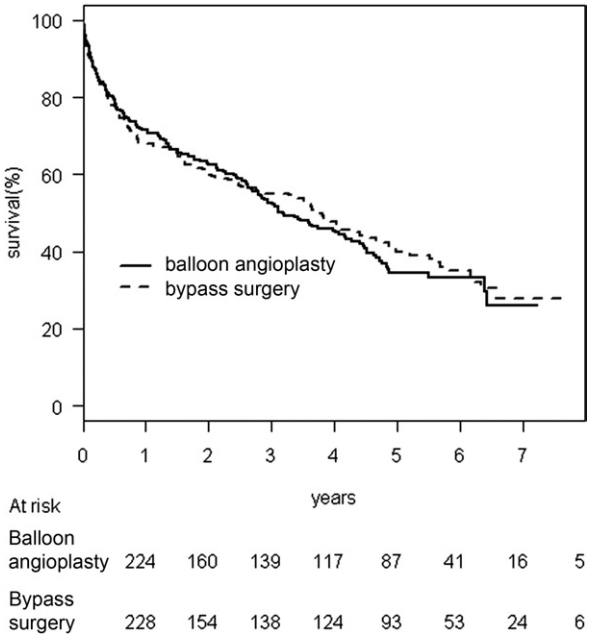

Fig 2. Curves show amputation-free survival in trial patients randomized to a bypass surgery-first or ballon angioplasty-first revascularization strategy.

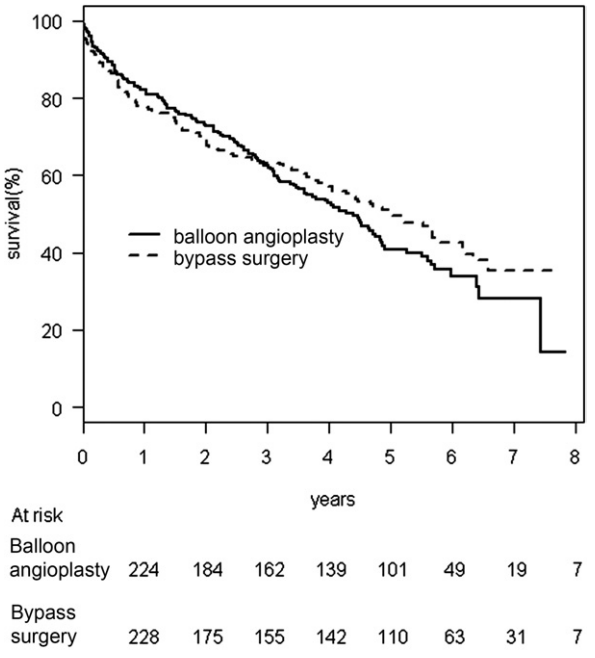

Fig 3. Curves show overall survival in trial patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy.

standard of care for most patients with lower limb ischemia.[54,55]

The BASIL trial aimed to determine whether a BSX-first or a BAP-first revascularization strategy in patients with SLI due to infrainguinal arterial disease was associated with a better outcome in terms of AFS, OS, HRQL, and use of hospital resources.[40] A preliminary analysis of the BASIL trial reported in 2005 indicated that short-term clinical outcomes from the two strategies were similar but that surgery was more morbid and was approximately one-third more expensive during the first 12 months.[35]

There was, however, 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 randomized to surgery. Although this difference was statistically significant, the 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.

To confirm or refute this apparent long-term advantage for surgery, further funding was obtained from the HTA to allow trial patients to be monitored for a further 2.5 years. This additional follow-up period was chosen on the basis of a careful statistical power calculation based on observed and anticipated events rates. The final ITT analysis of the BASIL trial presented here was, of course, conducted according to a prespecified statistical plan that was agreed to before the additional follow-up data became available.

When comparing open surgery with minimally invasive (endovascular) alternatives, trialists often try 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 about whether to subject a usually elderly and unfit patient with SLI to a lesser, arguably safer treatment now—such as BAP—at the risk of possibly compromising long-term outcomes of amputation and death can be difficult to analyze statistically within the confines of a RCT. As discussed subsequently, the correct interpretation of the data—and so the appropriate treatment for each individual patient—will largely depend on the time scale under consideration.

The main findings of the final ITT analysis. A review of the BASIL trial cohort and the follow-up period as a whole found no significant difference in AFS and OS between the two strategies, which some might view as a negative result and of no great interest. However, such a perspective overlooks the key purpose of, and outcomes from, the trial extension and time-dependent survival analysis prespecified in the statistical plan.

In the short term, BSX is nonsignificantly more hazardous than BAP and is more expensive; so a BAP-first strategy appears advisable given a 1- to 2-year perspective. In the longer term, however, BAP is significantly more hazardous in terms of OS than BSX. For those patients in whom a longer-term perspective is appropriate, a BSX-first strategy appears advisable; especially because in the longer term there is no significant difference in HRQOL or costs between the two treatments.[40]

Thus, patients who survived for 2 years and who were initially randomized to BSX gained a significant 7 months of additional life expectancy and an additional nonsignificant 6 months of amputation-free life expectancy over the

subsequent follow-up period compared with those randomized to BAP. Although these may not seem large differences, in the context of a condition with a very poor overall prognosis that is worse than many common malignancies, affected patients and physicians appear likely to view them as meaningful gains in life and limb.

A possible explanation for the long-term survival benefit after BSX might have been the survival of the fitter patients into the second period. However, this explanation is unlikely because the observed differences in OS in the period after 2 years were not attenuated by adjustment for covariates found to be predictive of outcome at baseline.[56]

Initial perusal of trial data not presented here suggests that factors that may possibly explain the long-term survival benefit for BSX include the quality of medical care and follow-up, enrollment in graft surveillance programs, and a more complete and durable revascularization as judged by hemodynamic indices, relief of symptoms, and healing of minor amputations. At the present time, however, this remains mere (although we think reasonable) speculation. The influence of these factors on outcomes is being analyzed and will be the subject of further separate reports in due course.

SLI imposes serious health and economic burdens in all developed countries and in 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 I evidence. The BASIL trial suggests that a BSX-first strategy should normally be regarded as the treatment of choice for the 75% of SLI patients who are estimated likely to live >2 years. Those unlikely to survive 2 years would seem better served by BAP in most cases. A predictive model based on easily obtainable baseline variables that attempts to estimate the chances of survival of "BASIL-like" patients to 2 years has been developed and is the subject of a further separate report.[56]

Improving the prognosis for severe limb ischemia. One possible, although somewhat "glass half empty" conclusion that might be drawn from the BASIL trial, and other multicenter or 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. From this perspective, we comment below on the trial outcomes and discuss what might be done differently going forward to try to improve this overall outlook.

Medical therapy. The BASIL trial has been criticized for reporting low levels of best medical therapy (BMT), such as antiplatelet agents and lipid-lowering therapy, at the time of randomization. There is no doubt that levels of BMT were disappointingly low and it would be comforting to think that it was a historical problem, now resolved, that simply reflected the timing of recruitment period 1999 to 2004. However, currently available data clearly show that is not the case; nor is it a phenomenon restricted to the UK health care system. Thus, more recent data from the UK[57] and North America show that there is still very considerable room for improvement when it comes to implementing evidence-based BMT[58,59] and, in particular, lipid-lowering treatment[58,60-62] in patients with PAD generally and those (highest risk) patients with SLI/CLI specifically. Such treatment will almost certainly increase overall survival and improve the results of surgical and endovascular interventions[63-65] at relatively little additional cost. This must surely be a highest priority for the global vascular community.

Outcomes of BSX. If physicians are going to be persuaded to take note of the BASIL trial data and recommendations in everyday clinical decision making, they will need to be persuaded that the results of BASIL reflects the current standard of care.[66] The problem is that the BASIL trial data set is not easily comparable against other data available in the literature because multicenter data are limited, no other RCTs are available for meta-analysis, and because of the particular characteristics of the patients eligible for and so admitted to the BASIL trial.

Currently, the largest and best data set of vein BSX for CLI comes from the Edifoligide for the Prevention of Infrainguinal Vein Graft Failure (PREVENT) III trial of a novel drug (edifoligide) hypothesized to reduce vein graft failure. Although the drug was not shown to be effective, the trial provided prospectively gathered, high-quality data on 1404 BSX procedures undertaken in >80 North American centers 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 short at only 12 months.[15] Furthermore, because of the hypothesis being tested,[67] the trial protocol mandated an especially intensive graft surveillance and reintervention program.

Nevertheless, reported short-term outcomes to 12 months for comparable PREVENT III and BASIL trial patients were similar.[15] AFS and OS rates in BASIL are also similar to those reported by others around the same period.[68,69] So it would seem that the BSX 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 centers of excellence may believe that their own results are substantially better than those usually reported from multicenter and registry studies.

The BASIL trial has been criticized for not specifying a standard follow-up protocol, which it has been suggested should have included (at least for the bypass grafts) mandatory duplex ultrasound-based graft surveillance and reintervention when certain hemodynamic criteria were met.[70,71] We have discussed this issue elsewhere[37] and point out that such an 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.[64,72]

Angioplasty outcomes. The BASIL trial has been criticized for the very low use of stents (9 cases). We have discussed this issue elsewhere.[37] Stenting of infrainguinal arteries was not regarded as standard of care in the UK at the time the trial. Even today, the evidence that stenting improves clinical outcomes compared with what can be achieved by angioplasty alone remains limited, especially in patients with SLI/CLI as opposed to intermittent claudication.[73]

The high failure rate and reintervention rate reported after BAP in BASIL has also been criticized.[37] However, our data are similar to that presented by others in patients with extensive multilevel disease.[6,24,27,39,74] It is a rapidly developing field, and new pharmacologic[30,75,76] and procedural and device developments are likely to improve the results of endovascular therapies for lower limb ischemia of all severities in the future.[1,74,77-82]

Choice of trial end points. The primary aim of the BASIL trial was to determine whether a BSX-first or a BAP-first revascularization 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 we finalized 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 revascularization; namely, to preserve limb and, so, life. We understand that AFS remains the end point required by the United States Food and Drug Administration for such studies.

During 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 thus design has become increasingly sophisticated. The thoughtful and transparent use of such end points can undoubtedly increase knowledge and understanding[83]; however, they can lead to a lack of clarity, an inability to compare different studies,[84] and even to concerns around the appropriateness of regulatory approval.[85-87]

The BASIL trial has been criticized for not using "patency" as the primary outcome. We have discussed this issue at length elsewhere.[37] In short, we wished specifically to compare two strategies not just two "one-off" procedures. As such, we thought powering or interpreting the trial in the context of measures of hemodynamic success (patency, ankle pressure) or other end points as surrogates for meaningful clinical outcomes would have been inappropriate.[20,88] Pragmatically, assessing patency after BAP in a uniform manner across 27 centers would have been logistically very difficult.

Choice of entry criteria. It has been suggested that the BASIL trial cannot be usefully generalized to the majority of patients with CLI. As very clearly stated throughout the article, even in the very title of the trial itself, this was emphatically not a trial of patients with "critical limb ischemia" as defined by the European Consensus Document, which was the competent document in the UK at the time the trial protocol was finalized in 1998.[36] Rather, the patients admitted to BASIL had "severe limb ischemia," which is the same as the European Consensus Document definition of CLI but, crucially, without the requirement to have an ankle pressure <50 mm Hg. This is perhaps a subtle but, nevertheless, a very important distinction that needs to be fully grasped in order 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 patients, and not just CLI, patients to the BASIL trial for a number of reasons:

First, 50 mm Hg is arguably an arbitrary cutoff. Does a patient who requires opiate analgesia for rest pain and with a gangrenous toe not have limb-threatening ischemia and not require immediate or early revascularization just because the ankle pressure is 60 mm Hg?

Second, measurement of ankle pressure and pressure indices in these patients is subject to interobserver and intraobserver variation.[89] Does a patient have limb-threatening ischemia that requires immediate or early revascularization on a day when the ankle pressure is measured at 45 mm Hg but not on another day when it is 55 mm Hg?

Third, when compared with BSX, BAP might have the most to offer to those at the better end of the spectrum of patients with rest pain and tissue loss. Many of these patients will require immediate or early revascularization to relieve severe pain or heal tissue loss, or both, but their ankle pressure will be >50 mm Hg. Would excluding such patients on the basis of an arbitrary hemodynamic cutoff from a trial where one of the arms was angioplasty make any sense?

Fourth, it became clear from our Delphi consensus studies that only a small proportion of patients with true "CLI" were deemed by vascular surgeons and interventionalists at that time to have a pattern of disease that they believed was equally suitable for BAP and BSX (gray area of clinical equipoise).[33,34]

Furthermore, at the time the BASIL trial was designed, Wolfe and Wyatt[90] from the UK had recently written an influential report describing what they termed "subcritical limb ischemia" (SCLI), which they defined as rest pain and ankle pressure >40 mm Hg, and they redefined CLI as tissue loss or ankle pressure <40 mm Hg, or both. These authors recommended on the basis of an analysis of 20 publications containing >6000 patients that future studies should stratify by SCLI/CLI because the two groups had very different patterns of disease, responses to treatment, and outcomes. More recently, other respected authorities have also recognized a similar group of patients who occupy a poorly defined hemodynamic area between disabling claudication and true CLI.[91]

Impressed by these scientific and logistic arguments, we chose to use the term "severe limb ischemia" (SLI) 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 stratified the randomization according to whether the patient had rest pain only or tissue loss also and by whether their ankle pressure was <50 mm Hg. We chose 50 mm Hg rather than 40 mm Hg to comply with ECD CLI guidelines.

In fact, 336 of 452 (74.3%) of the BASIL patients had tissue loss, which is 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 mm Hg, and 137 had an ankle pressure <50 mm Hg. As expected from the randomization process, these proportions were the same in both trial arms.

So, although it is quite true that the BASIL trial describes a group of patients who had, overall, less severe disease than studies where the 50 mm Hg is strictly adhered to, we think:

1. the admission criteria were clear;
2. the admission criteria were appropriate given the aims of the trial;
3. all the patients randomized were thought at the time of randomization to require early or immediate revascularization to relieve pain or heal tissue loss, or both, and were quite clearly not, as has been suggested, only claudicant patients (this is discussed further below); and
4. because BASIL reported transparently in detail the clinical and anatomic (angiographic)[39] characteristics of the randomized patients, physicians will be able to make an informed judgment about the extent to which their patients are similar to or different from those described here (this is discussed further below).

It has been suggested that many of the patients did not actually have true limb-threatening ischemia because not all patients went forward to immediate revascularization.[37] The number of patients who did not receive timely intervention was, in reality, small. In some cases, this was because the patient's condition deteriorated and the patient became unfit, especially for BSX; such patients fared badly. In other patients the ischemic pain or tissue loss improved with best medical and nursing care so that immediate revascularization was not required or was 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 revascularization 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.[92] We believe the BASIL data reflect the clinical realities of looking after this group of patients and demonstrate the value of developing predictive tools that can help physicians match the available treatments to individual patient's needs and circumstances.[56]

Patient selection and trial generalizability. At the same time, the BASIL trial has been criticized 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 a too heterogeneous a group of patients to be randomized (not selective enough). We were well aware that in common with every other RCT, there was going to be a trade-off when the BASIL trial was designed between purity of sampling and generalizability that could never be fully resolved to everyone's satisfaction.

The BASIL trial audit[35] found that 50% of patients presenting to six major UK vascular units with SLI due to infrainguinal disease were not considered suitable for, or to require, or to agree to immediate or early revascularization. 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" revascularization rate in other countries to be determined.[15,93] The BASIL trial has been almost uniquely transparent in placing the revascularized patients with the total population of consecutive patients presenting with SLI to the major participating centers. Until data to the contrary are reported, we think the BASIL audit data are likely to reflect data found in many other health care economies, especially where, unlike in the UK, access to care is dependent upon an ability to pay.

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

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 and interventionalists working according to their preferred methods in a large number of centers but then, crucially, to apply the rigor of randomization to the treatment received. It is the polar opposite of the single-surgeon, single-center experiences of treating a more homogenous group of patients in a highly standardized 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 "gray area of clinical equipoise."

In this respect the BASIL trial is no different from, for example, the carotid and aortic aneurysm trials that now guide intervention in those areas. Specifically, the BASIL trial compared (for the first and only time in a randomized manner) a BSX-first strategy with a BAP-

first strategy in patients who required and were fit for immediate or early revascularization for SLI due to infrainguinal disease and who, in the opinion the responsible surgeon and interventionalist, could be equally well treated by either BSX or BAP (the gray area of equipoise). So, of course, to be eligible for admission to the trial the patient had to have:

1. SLI due to infrainguinal disease;
2. require and be fit for immediate or early revascularization by either means; and
3. have a clinical and anatomic (angiographic) pattern of disease that led both the surgeon and the interventionalist to believe there was a 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) to be better treated by BSX, by BAP, with best medical and nursing care only, or by primary amputation. Such patients could not therefore be randomized by those physicians. The only other "selection" was that the patients had to be able and willing to give fully informed written consent. Given the nature of the patients and the two treatments on offer, a remarkably high proportion (about 70%) of eligible patients agreed to be randomized; this is a great credit to the vascular teams in the 27 centers.

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 randomize patients who were suitable for both treatment strategies and in whom there was genuine doubt about 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 "gray 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.[33,34]

Power of the trial. The power of the BASIL trial has been described as "marginal," with which we would 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.[35] In fact, these overall estimates turned out not to be unreasonable, and 452 patients were randomized; of whom only 4 were lost to follow-up.

The other important point is that the real power of a trial depends more on the number of end points than on the number of patients randomized; and BASIL patients provided no shortage of end points (amputations, deaths). But, of course, if one chooses to embark on subgroup analysis, then the power weakens; we have been careful not to do this. We have also been careful not to over-interpret 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.

Prosthetic grafts. Some have argued that it would have been better if the trial had excluded patients requiring prosthetic grafts. This is an issue that the trial investigators and participants considered carefully when designing the trial in the late 1990s.[37] At that time, however, it was common practice to use prosthetic grafts, usually with some form of venous cuff or collar, in SLI patients. Such surgery is still undertaken in the UK and elsewhere, although one suspects in smaller numbers than a decade ago. Excluding prosthetic grafts would probably have improved the results of surgery but may have led to accusations of cherry picking and bias from the interventional community. It seems likely to us that the interventional community would have "retaliated" by requesting that certain high-risk angioplasty cases be removed from the analysis. Instead, we have conducted a large pragmatic multicenter RCT where all angioplasty and all surgical outcomes have been analyzed by ITT.

By including prosthetic grafts and by also offering a "by-treatment-received" analysis in a separate article,[37] we have also been able to draw (with appropriate caveats) some conclusions about the relative merits of vein vs prosthetic bypass compared with angioplasty. However, we must be very careful not to over-interpret nonrandomized data.

CONCLUSIONS

Much of the available literature gives the impression that every patient who presents with SLI/CLI can and should undergo revascularization and that the results of those revascularizations are largely good. In reality, 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 treatment and nursing care.[92,94] Furthermore, attempts at revascularization often fail, and many SLI/CLI patients with a very limited life expectancy and HRQOL are not well served by, often repeated, attempts at limb salvage.[95-98]

Although AFS is an appropriate and unambiguous primary trial end point, it does not give much information about the quality of revascularization. It is quite possible for a patient to enjoy a reasonable HRQOL with a primary amputation, especially if the patient's premorbid mobility status was already limited, and for another patient to have a very poor QOL due to chronic pain and wound problems, despite an apparently successful revascularization.[88,97-99] The often-assumed inverse relationship between revascularization and amputation rates has not been borne out in an analysis of recent UK data.[100]

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.[1,43,88,90,91,95-98,101] 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 analyzed and will be the subject of further separate reports in due course.

Going forward, the BASIL investigators have also joined with others under the auspices of the Society for Vascular Surgery (SVS) to establish a working group to examine the data that might support objective performance goals (OPG) for current and future CLI therapies. In so doing, the group recognizes that large sample sizes are required to examine safety and efficacy, especially within critical subgroups. Data contributed from BASIL and other prospective multicenter studies are currently being used towards these ends.[102,103]

Summary of BASIL trial recommendations. The BASIL trial suggests that those SLI patients who are likely to live ≥2 years are probably better served by a BSX-first strategy, preferably with vein.[37] Those SLI patients who are unlikely to live 2 years, and possibly those in whom vein is not available for bypass, are probably better served by a BAP-first strategy because they are unlikely to survive to reap the longer-term benefits of surgery, they may be more likely to suffer surgical morbidity and mortality, and because angioplasty is significantly less expensive than surgery in the short-term.

REFERENCES

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg 2007;33(suppl 1):S1-75.
2. Axisa B, Fishwick G, Bolia A, Thompson MM, London NJ, Bell PR, Naylor AR. Complications following peripheral angioplasty. Ann R Coll Surg Engl 2002;84:39-42.
3. Shaw MB, DeNunzio M, Hinwood D, Nash R, Callum KG, Braithwaite BD. The results of subintimal angioplasty in a district general hospital. Eur J Vasc Endovasc Surg 2002;24:524-7.
4. Loftus IM, Hayes PD, Bell PR. Subintimal angioplasty in lower limb ischaemia. J Cardiovasc Surg 2004;45:217-29.
5. Jamsen T, Tulla H, Manninen H, Raisanen H, Lahtinen S, Aittola V, et al. Results of infrainguinal bypass surgery: an analysis of 263 consecutive operations. Ann Chir Gynaecol 2001;90:92-9.
6. Dougherty MJ, Young LP, Calligaro KD. One hundred twenty-five concomitant endovascular and open procedures for lower extremity arterial disease. J Vasc Surg 2003;37:316-22.
7. Nguyen LL, Conte MS, Menard MT, Gravereaux EC, Chew DK, Donaldson MC, et al. Infrainguinal vein bypass graft revision: factors affecting long-term outcome. J Vasc Surg 2004;40:916-23.
8. Morgan JH 3rd, Wall CE Jr, Christie DB, Harvey RL, Solis MM. The results of superficial femoral, popliteal, and tibial artery stenting for peripheral vascular occlusive disease. Am Surg 2005;71:905-9.
9. Abdul Raouf A, Rouleau Y, Clement A, Le Roux P, Genay P, Ricco JB. Endoluminal angioplasty of the popliteal artery. Review of 54 consecutive patients. Eur J Vasc Endovasc Surg 2005;30:610-3.
10. Smith BM, Stechman M, Gibson M, Torrie EP, Magee TR, Galland RB. Subintimal angioplasty for superficial femoral artery occlusion: poor patency in critical ischaemia. Ann R Coll Surg Engl 2005;87:361-5.
11. Bolia A. Subintimal angioplasty in lower limb ischaemia. J Cardiovasc Surg 2005;46:385-94.
12. Nowygrod R, Egorova N, Greco G, Anderson P, Gelijns A, Moskowitz A, et al. Trends, complications, and mortality in peripheral vascular surgery. J Vasc Surg 2006;43:205-16.
13. Vraux H, Bertoncello N. Subintimal angioplasty of tibial vessel occlusions in critical limb ischaemia: a good opportunity? Eur J Vasc Endovasc Surg 2006;32:663-7.
14. Awad S, Karkos CD, Serrachino-Inglott F, Cooper NJ, Butterfield JS, Ashleigh R, et al. The impact of diabetes on current revascularisation practice and clinical outcome in patients with critical lower limb ischaemia. Eur J Vasc Endovasc Surg 2006;32:51-9.
15. Conte MS, Bandyk DF, Clowes AW, Moneta GL, Seely L, Lorenz TJ, et al. Results of PREVENT III: a multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery. J Vasc Surg 2006;43:742-751.
16. Lu XW, Idu MM, Ubbink DT, Legemate DA. Meta-analysis of the clinical effectiveness of venous arterialization for salvage of critically ischaemic limbs. Eur J Vasc Endovasc Surg 2006;31:493-9.
17. Bosiers M, Hart JP, Deloose K, Verbist J, Peeters P. Endovascular therapy as the primary approach for limb salvage in patients with critical limb ischemia: experience with 443 infrapopliteal procedures. Vascular 2006;14:63-9.
18. Kudo T, Chandra FA, Kwun WH, Haas BT, Ahn SS. Changing pattern of surgical revascularization for critical limb ischemia over 12 years: endovascular vs. open bypass surgery. J Vasc Surg 2006;44:304-13.
19. Engelhardt M, Bruijnen H, Scharmer C, Jezdinsky N, Wolfle K. Improvement of quality of life six months after infrageniculate bypass surgery: diabetic patients benefit less than non-diabetic patients. Eur J Vasc Endovasc Surg 2006;32:182-7.
20. Taylor SM, Cull DL, Kalbaugh CA, Cass AL, Harmon SA, Langan EM 3rd, et al. Critical analysis of clinical success after surgical bypass for lower-extremity ischemic tissue loss using a standardized definition combining multiple parameters: a new paradigm of outcomes assessment. J Am Coll Surg 2007;204:831-8.
21. Eskelinen E, Lepantalo M. Role of infrainguinal angioplasty in the treatment of critical limb ischaemia. Scan J Surg 2007;96:11-6.
22. Lepantalo M, Eskelinen E. Outcome of infrapopliteal bypass in the elderly. Acta Chir Bel 2007;107:1-7.
23. Graziani L, Silvestro A, Bertone V, Manara E, Alicandri A, Parrinello G, et al. Percutaneous transluminal angioplasty is feasible and effective in patients on chronic dialysis with severe peripheral artery disease. Nephrol Dial Transplant 2007;22:1144-9.
24. Bargellini I, Petruzzi P, Scatena A, Cioni R, Cicorelli A, Vignali C, et al. Primary infrainguinal subintimal angioplasty in diabetic patients. Cardiovasc Intervent Radiol 2008;31:713-22.
25. Lantis J, Jensen M, Benvenisty A, Mendes D, Gendics C, Todd G. Outcomes of combined superficial femoral endovascular revascularization and popliteal to distal bypass for patients with tissue loss. Ann Vasc Surg 2008;22:366-71.
26. Malmstedt J, Leander K, Wahlberg E, Karlstrom L, Alfredsson L, Swedenborg J. Outcome after leg bypass surgery for critical limb ischemia is poor in patients with diabetes: a population-based cohort study. Diabetes Care 2008;31:887-92.
27. Habib SB, Sonoda L, See TC, Ell PJ, Groves AM. How do patients perceive the benefits and risks of peripheral angioplasty? Implications for informed consent. J Vasc Intervent Radiol 2008;19:177-81.
28. Nguyen LL, Hevelone N, Rogers SO, Bandyk DF, Clowes AW, Moneta GL, et al. Disparity in outcomes of surgical revascularization for limb salvage: race and gender are synergistic determinants of vein graft failure and limb loss. Circulation 2009;119:123-30.
29. Mahmud E, Cavendish JJ, Salami A. Current treatment of peripheral arterial disease: role of percutaneous interventional therapies. J Am Coll Cardiol 2007;50:473-90.
30. Tang GL, Morasch MD. Role of stents, drug-eluting stents, and stent-grafts in treatment of infrainguinal arterial disease. Semin Vasc Surg 2007;20:37-41.
31. Rogers JH, Laird JR. Overview of new technologies for lower extremity revascularization. Circulation 2007;116:2072-85.
32. Met R, Van Lienden KP, Koelemay MJ, Bipat S, Legemate DA, Reekers JA. Subintimal angioplasty for peripheral arterial occlusive disease: a systematic review. Cardiovasc Intervent Radiol 2008;31:687-97.

33. Bradbury AW, 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;24:411-6.
34. Bradbury A, Wilmink T, Lee AJ, Bell J, Prescott R, Gillespie I, et al. Bypass versus angioplasty to treat severe limb ischemia: factors that affect treatment preferences of UK surgeons and interventional radiologists. J Vasc Surg 2004;39:1026-32.
35. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet 2005;366:1925-34.
36. Second European consensus document on chronic critical leg ischemia. Circulation 1991;84(suppl 4):1-26.
37. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FGR, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: analysis of amputation free and overall survival by treatment received. J Vasc Surg 2010;51(Suppl 10):18S-31S.
38. Bollinger A, Breddin K, Hess H, Heystraten FM, Kollath J, Konttila A, et al. Semi-quantitative assessment of lower limb atherosclerosis from routine angiographic images. Atherosclerosis 1981;38:339-46.
39. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FGR, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: a description of the severity and extent of disease using the Bollinger angiogram scoring method and the TransAtlantic Inter-Society Consensus II classification. J Vasc Surg 2010;51(Suppl 10):32S-42S.
40. Forbes JF, Adam DJ, Bell J, Fowkes FGR, Gillespie I, Raab GM, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: health-related quality of life outcomes, resource utilization, and cost-effectiveness analysis. J Vasc Surg 2010;51(Suppl 10):43S-51S.
41. Karrison T. Restricted mean life with adjustment for covariates. J Am Stat Assoc 1987;82:1169-76.
42. Desai TR, Meyerson SL, Skelly CL, MacKenzie KS, Bassiouny HS, Katz D, et al. Patency and limb salvage after infrainguinal bypass with severely compromised ("blind") outflow. Arch Surg 2001;13:635-42.
43. Al-Omran M, Tu JV, Johnston KW, Mamdani MM, Kucey DS. Outcome of revascularization procedures for peripheral arterial occlusive disease in Ontario between 1991 and 1998: a population-based study. J Vasc Surg 2003;38:279-88.
44. Atar E, Siegel Y, Avrahami R, Bartal G, Bachar GN, Belenky A. Balloon angioplasty of popliteal and crural arteries in elderly with critical chronic limb ischemia. Eur J Radiol 2005;53:287-92.
45. Abando A, Akopian G, Katz SG. Patient sex and success of peripheral percutaneous transluminal arterial angioplasty. Arch Surg 2005;140: 757-61.
46. DeRubertis BG, Faries PL, McKinsey JF, Chaer RA, Pierce M, Karwowski J, et al. Shifting paradigms in the treatment of lower extremity vascular disease: a report of 1000 percutaneous interventions. Ann Surg 2007;246:415-22.
47. Lipsitz EC, Ohki T, Veith FJ, Suggs WD, Wain RA, Cynamon J, et al. Does subintimal angioplasty have a role in the treatment of severe lower extremity ischemia? J Vasc Surg 2003;37:386-91.
48. Tefera G, Turnipseed W, Tanke T. Limb salvage angioplasty in poor surgical candidates. Vasc Endovasc Surg 2003;37:99-104.
49. DeRubertis BG, Pierce M, Ryer EJ, Trocciola S, Kent KC, Faries PL. Reduced primary patency rate in diabetic patients after percutaneous intervention results from more frequent presentation with limb-threatening ischemia. J Vasc Surg 2008;47:101-8.
50. Ishii H, Kumada Y, Toriyama T, Aoyama T, Takahashi H, Yamada S, et al. Cilostazol improves long-term patency after percutaneous transluminal angioplasty in hemodialysis patients with peripheral artery disease. Clin J Am Soc Nephrol 2008;3:1034-40.
51. Werk M, Langner S, Reinkensmeier B, Boettcher HF, Tepe G, Dietz U, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. Circulation 2008;118:1358-65.
52. Perera GB, Lyden SP. Current trends in lower extremity revascularization. Surg Clin North Am 2007;87:1135-47.
53. Zeller T. Current state of endovascular treatment of femoro-popliteal artery disease. Vascular Medicine 2007;12:223-34.
54. White CJ, Gray WA. Endovascular therapies for peripheral arterial disease: an evidence-based review. Circulation 2007;116:2203-15.
55. Lee LK, Kent KC. Infrainguinal occlusive disease: endovascular intervention is the first line therapy. Advance Surg 2008;42:193-204.
56. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FGR, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: a survival prediction model to facilitate clinical decision making. J Vasc Surg 2010;51(Suppl 10):52S-68S.
57. Khan S, Flather M, Mister R, Delahunty N, Fowkes G, Bradbury A, et al. Characteristics and treatments of patients with peripheral arterial disease referred to UK vascular clinics: results of a prospective registry. Eur J Vasc Endovasc Surg 2007;33:442-50.
58. Schanzer A, Hevelone N, Owens CD, Beckman JA, Belkin M, Conte MS. Statins are independently associated with reduced mortality in patients undergoing infrainguinal bypass graft surgery for critical limb ischemia. J Vasc Surg 2008;47:774-78.
59. Feringa HH, Bax JJ, Hoeks S. van Waning VH, Elhendy A, Karagiannis S, et al. A prognostic risk index for long-term mortality in patients with peripheral arterial disease. Arch Intern Med 2007;167:2482-9.
60. Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. Cochrane Database Syst Rev 2007:CD000123.
61. Feringa HH, Karagiannis SE, van Waning VH, Boersma E, Schouten O, Bax JJ, et al. The effect of intensified lipid-lowering therapy on long-term prognosis in patients with peripheral arterial disease. J Vasc Surg 2007;45:936-43.
62. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg 2007;45: 645-54.
63. Collins TC, Souchek J, Beyth RJ. Benefits of antithrombotic therapy after infrainguinal bypass grafting: a meta-analysis. Am J Med 2004; 117:93-9.
64. Carter A, Murphy MO, Halka AT, Turner NJ, Kirton JP, Murray D, et al. The natural history of stenoses within lower limb arterial bypass grafts using a graft surveillance program. Ann Vasc Surg 2007;21:695-703.
65. Welten GM, Schouten O, Hoeks SE, Chonchol M, Vidakovic R, van Domburg RT, et al. Long-term prognosis of patients with peripheral arterial disease: a comparison in patients with coronary artery disease. J Am Coll Cardiol 2008;51:1588-96.
66. Owens CD, Ho KJ, Conte MS. Lower extremity vein graft failure: a translational approach. Vasc Med 2008;13:63-74.
67. Conte MS, Lorenz TJ, Bandyk DF, Clowes AW, Moneta GL, Seely BL. Design and rationale of the PREVENT III clinical trial: edifoligide for the prevention of infrainguinal vein graft failure. Vasc Endovasc Surg 2005;39:15-23.
68. Feinglass J, Pearce WH, Martin GJ, Gibbs J, Cowper D, Sorensen M, et al. Postoperative and amputation-free survival outcomes after femorodistal bypass grafting surgery: findings from the Department of Veterans Affairs National Surgical Quality Improvement Program. J Vasc Surg 2001;34:283-90.
69. Faries PL, Arora S, Pomposelli FB Jr, Pulling MC, Smakowski P, Rohan DI, et al. The use of arm vein in lower-extremity revascularization: results of 520 procedures performed in eight years. J Vasc Surg 2000;31:50-9.
70. Landry GJ, Moneta GL, Taylor LM Jr, Edwards JM, Yeager RA, Porter JM. Long-term outcome of revised lower-extremity bypass grafts. J Vasc Surg 2002;35:56-62.
71. Landry GJ, Liem TK, Mitchell EL, Edwards JM, Moneta GL. Factors affecting symptomatic vs. asymptomatic vein graft stenoses in lower extremity bypass grafts. Arch Surg 2007;142:848-53.
72. Davies AH, Hawdon AJ, Sydes, MR, Thompson SG on Behalf of the VGST Participants. Is duplex surveillance of value after leg vein bypass grafting? Principal Results of the Vein Graft Surveillance Randomised Trial (VGST). Circulation 2005;112:1985-91.
73. Kasapis C, Henke PK, Chetcuti SJ, Koenig GC, Rectenwald JE, Krishnamurthy VN, Grossman PM, Gurm HS. Routine stent implantation vs. percutaneous transluminal angioplasty in femoropopliteal artery disease: a meta-analysis of randomized controlled trials. Eur Heart J 2009;30:44-55.

74. Bosiers M, Cagiannos C, Deloose K, Verbist J, Peeters P. Drug-eluting stents in the management of peripheral arterial disease. Vasc Health Risk Manage 2008;4:553-9.
75. Koppensteiner R, Spring S, Amann-Vesti BR, Meier T, Pfammatter T, Rousson V, Banyai M, van der Loo B. Low-molecular-weight heparin for prevention of restenosis after femoropopliteal percutaneous transluminal angioplasty: a randomized controlled trial. J Vasc Surg 2006; 44:1247-53.
76. Schindler C, Mueller A, Bramlage P, Boecking W, Kirch W, Schweizer J. Comparison of selective AT1-receptor blockade versus ACE inhibition for restenosis prophylaxis in patients with peripheral occlusive arterial disease after stent angioplasty: a randomized, controlled, proof-of-concept study. Angiology 2008 58:710-6.
77. Jacobs DL, Motaganahalli RL, Cox DE, Wittgen CM, Peterson GJ. True lumen re-entry devices facilitate subintimal angioplasty and stenting of total chronic occlusions: initial report. J Vasc Surg 2006;43: 1291-6.
78. Zeller T, Tiefenbacher C, Steinkamp HJ, Langhoff R, Wittenberg G, Schluter M, Buergelin K, Rastan A, Krumsdorf U, Sixt S, Schulte CL, Tubler T, Krankenberg H. Nitinol stent implantation in TASC A and B superficial femoral artery lesions: the Femoral Artery Conformexx Trial (FACT). J Endovasc Ther 2008;15:390-8.
79. Krankenberg H, Schluter M, Steinkamp HJ, Burgelin K, Scheinert D, Schulte KL, et al. Nitinol stent implantation versus percutaneous transluminal angioplasty in superficial femoral artery lesions up to 10 cm in length: the femoral artery stenting trial (FAST). Circulation 2007;116:285-92.
80. Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. N Engl J Med 2006;354:1879-88.
81. Schmehl J, Tepe G. Current status of bare and drug-eluting stents in infrainguinal peripheral vascular disease. Expert Rev Cardiovasc Ther 2008;6:531-8.
82. Tan JW, Yeo KK, Laird JR. Excimer laser assisted angioplasty for complex infrainguinal peripheral artery disease: a 2008 update. J Cardiovasc Surg 2008;49:329-40.
83. Rocha-Singh KJ, Jaff MR, Crabtree TR, Bloch DA, Ansel G. VIVA Physicians, Inc. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Cathete Cardiovasc Inter 2007;69: 910-9.
84. Diehm N, Baumgartner I, Jaff M, Do DD, Minar E, Schmidli J, et al. A call for uniform reporting standards in studies assessing endovascular treatment for chronic ischaemia of lower limb arteries. Eur Heart J 2007;28:798-805.
85. Weinberger J, Rundback JH, Ratchford EV. Regulatory approval of peripheral endovascular revascularization devices in the United States: is the horse still in the barn? Am J Therapeut 2005;12:186-91.
86. Diehm N, Diehm C, Kalka C, Dick F. Peripheral endovascular revascularization trials: high noon for uniform reporting standards. Acta Chir Bel 2008;108:382-5.
87. Diehm N, Pattynama PM, Jaff MR, Cremonesi A, Becker GJ, Hopkins LN, et al. Clinical endpoints in peripheral endovascular revascularization trials: a case for standardized definitions. Eur J Vasc Endovasc Surg 2008;36:409-19.
88. Goshima KR, Mills JL Sr, Hughes JD. A new look at outcomes after infrainguinal bypass surgery: traditional reporting standards systematically underestimate the expenditure of effort required to attain limb salvage. J Vasc Surg 2004;39:330-5.
89. Caruana MF, Bradbury AW, Adam D. The validity, reliability, reproducibility and extended utility of ankle to brachial pressure index in current vascular surgical practice. Eur J Vasc Endovasc Surg 2005;29: 443-51.
90. Wolfe JH, Wyatt MG. Critical and subcritical ischaemia. Eur J Vasc Endovasc Surg 1997;13:578-82.
91. White JV, Rutherford RB, Ryjewski C. Chronic subcritical limb ischemia: a poorly recognized stage of critical limb ischemia. Semin Vasc Surg 2007;20:62-7.
92. Brass EP, Anthony R, Dormandy J, Hiatt WR, Jiao J, Nakanishi A, et al. Circulase investigators. Parenteral therapy with lipo-ecraprost, a lipid-based formulation of a PGE1 analog, does not alter six-month outcomes in patients with critical leg ischemia J Vasc Surg 2006;43:752-9.
93. Nehler MR, Brass EP, Anthony R, Dormandy J, Jiao J, McNamara TO, et al. Adjunctive parenteral therapy with lipo-ecraprost, a prostaglandin E1 analog, in patients with critical limb ischemia undergoing distal revascularization does not improve 6-month outcomes. J Vasc Surg 2007;45: 953-61.
94. Marston WA, Davies SW, Armstrong B, Farber MA, Mendes RC, Fulton JJ, et al. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. J Vasc Surg 2006;44:108-14.
95. Nehler MR, Peyton BD. Is revascularization and limb salvage always the treatment for critical limb ischemia? J Cardiovasc Surg 2004;45: 177-84.
96. Reed AB, Delvecchio C, Giglia JS. Major lower extremity amputation after multiple revascularizations: was it worth it? Ann Vasc Surg 2008;22:335-40.
97. Chung J, Bartelson BB, Hiatt WR, Peyton BD, McLafferty RB, Hopley CW, et al. Wound healing and functional outcomes after infrainguinal bypass with reversed saphenous vein for critical limb ischemia. J Vasc Surg 2006;43:1183-90.
98. Taylor SM. Current status of heroic limb salvage for critical limb ischemia. Am Surg 2008;74:275-84.
99. Novo S, Coppola G, Milio G. Critical limb ischemia: definition and natural history. Current Drug Targets Cardiovas Haematol Disord 2004;4:219-25.
100. McCaslin JE, Hafez HM, Stansby G. Lower-limb revascularization and major amputation rates in England. Br J Surg 2007;94:835-9.
101. Cao P, De Rango P. Endovascular treatment of peripheral arterial disease: so lld yet so far from evidence! Eur J Vasc Endovasc Surg 2009;37:501-3.
102. Conte MS, Geraghty PJ, Bradbury AW, Hevelone ND, Lipsitz SR, Moneta GL, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. J Vasc Surg 2009;50:1462-73.
103. Geraghty PJ, Matsumura JS, Conte MS. Premarket assessment of devices for treatment of critical limb ischemia: the role of Objective Performance Criteria and Goals. J Vasc Surg 2009;50:1459-61.

Submitted Feb 2, 2009; accepted Jan 24, 2010.

APPENDIX

BASIL trial Participants and Contributors

HTA grant applicants: Professor A. W. Bradbury (lead applicant), Mr D. J. Adam, Dr J. F. Forbes, Professor F. G. R. Fowkes, Dr I. Gillespie, Professor G. Raab, Professor C. V. Ruckley.

Writing Committee: Professor A. W. Bradbury, Sampson Gamgee Professor of Vascular Surgery, University of Birmingham and Honorary Consultant Vascular and Endovascular Surgeon, Heart of England NHS Foundation Trust: Principal investigator and corresponding author; all aspects of trial design, grant application, delivery, and analysis of the trial.

Mr D. J. Adam, Senior Lecturer in Vascular Surgery, University of Birmingham and Honorary Consultant Vascular and Endovascular Surgeon, Heart of England NHS Foundation Trust, Birmingham: data analysis and writing of the paper.

Dr J. Bell, BASIL Trial Coordinator: trial management, data collection, data analysis, and writing of the paper.

Dr J. F. Forbes, Reader in Health Economics, University of Edinburgh: grant coapplicant, trial design, data

analysis, and writing of the paper; special responsibility for HRQOL and health economics.

Professor F. G. R. Fowkes, Professor of Epidemiology, University of Edinburgh: grant coapplicant, trial design, data analysis, and writing of the paper.

Dr I. Gillespie, Consultant Interventional Radiologist, Edinburgh Royal Infirmary and Honorary Senior Lecturer, University of Edinburgh: grant coapplicant, trial design, data analysis, and writing of the paper.

Professor G. Raab, Professor of Statistics, Edinburgh Napier University: trial statistician; design of statistical plan, performance of the statistical analysis, and writing of the paper.

Professor C. V. Ruckley, Emeritus Professor of Vascular Surgery, University of Edinburgh: grant coapplicant, trial design, data analysis, and writing of the paper.

Data management and statistical analysis: Dr J. Bell (trial manager), Professor G. Raab.

Data Monitoring Committee: Professor G. D. O. Lowe (Chairman), Professor R. M. Greenhalgh, Dr A. Nicholson, Professor R. Prescott (Professor R. J. Prescott and Dr A. Lee prepared the data for the committee).

Trial Steering Committee: Professor A. W. Bradbury (Chairman), Dr R. Ashleigh, Dr M. Bain, Mr J. D. Beard, Ms J. Brittenden, Dr J. F. Forbes, Professor F. G. R. Fowkes, Dr P. Gaines, Dr I. Gillespie, Dr S. Girling, Dr K. McBride, Dr J. Moss, Professor G. Raab, Professor C. V. Ruckley, Professor G. Stansby, Mr G. Welch, Mr A. Wilmink, Mr D. J. Adam.

Angiogram assessment and scoring: Dr K. McBride, Dr R. Ashleigh.

Research nurses: G. Bate, J. Blundell, M. Burrows, J. Coleman, M. Cullen, C. Devine, L. Holmes, G. Horne, B. Hughes, J. Innes, M. Ireland, C. Judge, P. Morris-Vincent, H. Purdie, M. Roseborough, J. Simpson, R. Stuart, T. Uppal, B. Walsh, B. Watson, V. Wealleans, L. Wilson, S. Zito.

BASIL trial Participants

The following consultant vascular surgeons and interventional radiologists working at the following centres entered patients into the trial (number in brackets indicates number of patients entered into BASIL; *denotes center took part in the BASIL audit): P. Bachoo, J. Brittenden, G. Cooper, S. Cross, J. Engeset, J. Hussey, E. Macauley, P. Thorpe, ***Aberdeen Royal Infirmary (58)**; G. Stewart, K. Osbourne, Ayr Hospital (1); J. Moss, P. Nicholl, S. Silverman, J. Wingate, **City Hospital, Birmingham (9)**; D. Adam, B. Balasubramanian, A. Bradbury, P. Crowe, J. Ferrando, M. Gannon, M. Henderson, K. Makhdoomi, D. Mosquera, T. Wilmink, ***Heart of England NHS Foundation Trust (33)**; T. Buckenham, R. Chalmers, R. Dawson, S. Fraser, I. Gillespie, S. Ingram, A. Jenkins, J. Murie, Z. Raza, **Edinburgh Royal Infirmary (27)**; N. Jones, D. Lambert, T. Lees, R. Owen, J. Rose, G. Stansby, M. Wyatt, ***Freeman Hospital, Newcastle (21)**; D. Byrne, R. Edwards, A. MacKay, J. Moss, R. Quin, P. Rogers, **Gartnavel Hospital, Glasgow (23)**; D. Gilmour, D. Leiberman, D. McCarter, A. Reid, **Glasgow Royal Infirmary (1)**; S. Dodds, M. Cleesby, A. Jewkes, B. Jones, C. Nelson, A. Parnell, **Good Hope Hospital, Sutton Coldfield (11)**; P. Bell, A. Bolia, **Leicester Royal Infirmary (1)**; N. Chalmers, I. Mohan, V. Smyth, M. Walker, **Manchester Royal Infirmary (6)**; M. Collins, A. Garnham, G. Mackie, **New Cross Hospital, Wolverhampton (9)**; P. Stonebridge, J. Houston, **Ninewells Hospital, Dundee (1)**; M. Armon, J. Clarke, J. Cockburn, J. Colin, S. Girling, S. Scott-Barrett, P. Wilson, Y. Wilson, ***Norfolk & Norwich Hospital (60)**; J. Beard, T. Cleveland, P. Chan, P. Gaines, R. Lonsdale, J. Michaels, A. Nassif, R. Niar, J. Rochester, S. Thomas, R. Wood, ***Northern General Hospital, Sheffield (64)**; A. Ashour, V. Bhattachary, A. Nudawi, G. Timmons, **Queen Elizabeth Hospital, Gateshead (2)**; A. Howd, M. Fleet, H. Ireland, K. McBride, A. Milne, A. Turner, **Queen Margaret Hospital, Dunfermline (21)**; G. Ferguson, M. Onwudike, R. Razzaq, J. Tuck, **Royal Bolton Infirmary (5)**; D. Baker, G. Hamilton, F. Hyint, A. Platts, J. Tibballs, A. Watkinson, **Royal Free Hospital, London (3)**; K. Choji, R. Grimley, A. Jayatunga, R. Patel, J. Renny, S. Shiralkar, A. Wilinski, **Russells Hall Hospital, Dudley (20)**; M. Alner, M. Duddy, A. Edwards, M. Simms, S. Smith, R. Vohra, **Selly Oak Hospital, Birmingham (11)**; G. MacBain, R. Johnstone, G. Urquhart, G. Welch, **Southern General Hospital, Glasgow (10)**; D. Durrans, B. Gwynn, C. Willard, **Staffordshire General Hospital, Stafford (2)**; M. Thompson, R. Morgan, **St Georges Hospital, London (3)**; J. Patel, J. Scott, I. Spark, **St James Hospital, Leeds (2)**; K. Allen, A. Khan, J. Holland, **Walsall Manor Hospital, Walsall (4)**; R. Ashleigh, S. Butterfield, R. England, C. McCollum, A. Nasim, M. Welch, ***Wythenshawe Hospital, Manchester (44).**

The BASIL trial was only made possible by the enthusiasm and commitment of the trial centers and we thank all the health care personnel in those centers for their support of the study.