Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial

Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Analysis of amputation free and overall survival by treatment received

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Background: **An intention-to-treat analysis of randomized Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial data showed that initial randomization to a bypass surgery (BSX)-first strategy was associated with improvements in subsequent overall survival (OS) and amputation-free survival (AFS) of about 7 and 6 months, respectively. We describe the nature and timing of first, crossover, and reinterventions and examine AFS and OS by first treatment received. We also compare vein with prosthetic BSX and transluminal with subintimal balloon angioplasty (BAP) and examine outcomes from BSX after failed BAP.**

Methods: **We randomly assigned 452 patients with SLI due to infrainguinal disease in 27 United Kingdom hospitals to a BSX first (n = 228) or a BAP first (n = 224) revascularization strategy. All patients have been monitored for 3 years and more than half for >5 years. We prospectively collected data on every procedure, major amputation, and death.**

Results: **Patients randomized to BAP were more likely to have their assigned treatment first (94% vs 85%, $P = .01$, χ^2test). BAP had a higher immediate technical failure rate of 20% vs 2.6% ($P = .01$, χ^2test). By 12 weeks after randomization 9 BAP (4%) vs 23 BSX (10%) patients had not undergone revascularization; 3 BAP (1.3%) vs 13 BSX (5.8%) had undergone the opposite treatment first; and 35 BAP (15.6%) and 2 (0.9%) BSX had received the assigned treatment and then undergone the opposite treatment. BSX distal anastomoses were divided approximately equally between the above and below knee popliteal and crural arteries; most originated from the common femoral artery. About 25% of the grafts were prosthetic and >90% of vein BSX used ipsilateral great saphenous vein. Most (80%) BAP patients underwent treatment of the SFA alone (38%) or combined with the popliteal artery (42%) and crural arteries (20%). Outcome of vein BSX was better for AFS ($P = 0.003$) but not OS ($P = 0.38$, log-rank tests) than prosthetic BSX. There were no differences in outcome between approximately equal numbers of transluminal and subintimal BAP. AFS ($P = 0.006$) but not OS ($P = 0.06$, log rank test) survival was significantly worse after BSX after failed BAP than after BSX as a first revascularization attempt.**

Conclusions: **BAP was associated with a significantly higher early failure rate than BSX. Most BAP patients ultimately required surgery. BSX outcomes after failed BAP are significantly worse than for BSX performed as a first revascularization attempt. BSX with vein offers the best long term AFS and OS and, overall, BAP appears superior to prosthetic BSX. (J Vasc Surg 2010;51:18S-31S.)**

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] The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial remains the only multicenter, randomized controlled trial (RCT) to have compared a bypass surgery (BSX)-first and a balloon angioplasty (BAP)-first revascularization strategy for the treatment SLI due to infrainguinal disease.

An intention-to-treat (ITT) analysis of the BASIL trial has shown that BSX and BAP lead to similar amputation-free survival (AFS) and overall survival (OS) out to 2 years from randomization.[2] However, for those patients who survived for >2 years after intervention, initial randomization to BSX was associated with a significant increase of 7.3 months in restricted mean OS and a nonsignificant increase of 5.9 months in restricted mean AFS during the subsequent mean follow-up of 3.1 years (range, 1-7 years).[3] Hospital costs and health-related quality of life (HRQOL) were not significantly different between the two groups during the first 3 years.[4] These findings, based on an ITT analysis of randomized data, suggest that patients expected

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*The BASIL trial participants are listed in the Appendix.

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to live >2 years should usually be considered for BSX first, whereas those not expected to survive >2 years should normally be considered for BAP in the first instance.

Although most 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 revascularization 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 (BTR) analyses of RCTs have to be undertaken with very great care because the rigor of randomization has been lost and a degree of bias is therefore inevitable. However, surgical and interventional colleagues have urged us strongly to undertake a BTR analysis of the BASIL data. We recognize that such an approach is appropriate, provided it is interpreted with caution, and may increase the value of the trial to clinicians managing these challenging patients. So, here we present an analysis of the main clinical outcomes (AFS, OS) by the first intervention received and describe the nature and timing of first, crossover, and reinterventions. We also compare vein with prosthetic BSX and transluminal with subintimal BAP and examine outcomes from BSX after failed BAP.

METHODS

All patients who participated in this study 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 the International Standard Randomized Controlled Trials Number (ISRCTN) Scheme (Number 45398889).

Trial methods. The BASIL trial methods have been described in detail previously.[2,3] Briefly, between August 1999 and June 2004, consultant vascular surgeons and interventionalists in 27 United Kingdom (UK) hospitals randomized 452 patients with SLI, defined as rest pain and/or tissue loss (ulcer and/or gangrene) of arterial etiology present for more than 2 weeks, and who on diagnostic imaging had a pattern of disease which, in their joint opinion, could equally well be treated by either infrainguinal BSX or BAP, to a BSX-first or a BAP-first revascularization strategy. Responsible consultant vascular surgeons and interventionalists were encouraged to undertake the assigned procedure as soon as possible after patient randomization; were permitted to use their normal custom and practice with regard to preintervention assessment, the intervention itself, and postintervention follow-up; and were asked to record at the end of the procedure whether in their view it had been an immediate technical success.

Data on all first and reinterventions were prospectively collected, as were those on amputation of the trial limb at the transtibial level or above, and death from any cause. For the first year of follow-up, four dedicated research nurses travelled regularly to trial centers to collect data on randomized patients. Thereafter, the data were collected locally by the vascular teams. 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 on further procedures and primary outcomes. Where necessary, we also contacted primary care doctors and nurses. In addition, end point data on deaths, amputations, and further procedures were collected through national audit mechanisms.

Details of patients recruited in Scottish centers were also logged with the Information and Statistics Division (ISD) of the National Health Service in Scotland. All patients alive at the end of follow-up had their status confirmed by linkage to General Registry Office (Scotland) or the Office of National Statistics England death records. Hospital admissions for Scottish patients were obtained by record linkage to Scottish Morbidity Records (SMR-01). All patients have been followed-up for 3 years and more than 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 patient's outcome.[5,6]

Statistical analysis. For the survival analyses, patients with no report of survival were taken as censored at end February 2007 if their death information was from ISD, at end July 2007 if their death information was from Office of National Statistics, 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 randomization. Comparison of amputation-free survival and overall survival was by log-rank tests. Other associations were assessed by χ^2 and the Fisher exact test with tests for trend where appropriate.

Role of the funding source. The sponsor of the study (Health Technology Assessment, UK government funding) had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

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

RESULTS

Nature and timing of first attempted revascularization and subsequent procedures after randomization. Of the 228 patients randomized to BSX first, 195 (85%) underwent attempted surgery as their first procedure, and 5 underwent endarterectomy and vein patch rather than BSX. 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 patients, 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, giving an immediate failure rate of 5 of 195 (2.6%). Thus, 193 patients (84%) randomized to BSX underwent a completed surgical procedure as their first intervention, of which 188 were completed bypasses.[2]

Of the 224 patients randomized to BAP first, 216 (96%) underwent attempted BAP as their first procedure. Of these, 43 (20%) of these were deemed immediate technical failures.[2] In 10 patients this was because the vessel lumen could not be entered or the disease could not be completely crossed with a guidewire. The lesion was crossed subintimally in 18 patients, but the lumen could not be reentered. Two procedures were abandoned before a guidewire had been passed across the disease because the patient could not tolerate the procedure. Two procedures were terminated because of vessel perforation after a guidewire had been passed. One procedure was terminated immediately because the type of disease described as being present in the preoperative duplex ultrasound image was not present at the time of angiography. In a further 10 patients, there was immediate thrombosis of the BAP channel and in 6 there was also distal embolization that could not be rectified radiologically by means of thrombolysis or aspiration. All surgical and interventional procedures undertaken on the trial leg at any time during follow-up (range 3 to 7 years) are for the cohort as a whole and by trial arm are reported in Table I.

The cumulative number of treatments received by patients during the first 12 weeks from randomization is reported in Table II. By 12 weeks after randomization 9 (4%) BAP vs 23 (10%) BSX patients had not undergone revascularization; 3 (1.3%) BAP vs 13 (5.8%) BSX had undergone the opposite treatment first; and 35 (15.6%) BAP and 2 (0.9%) BSX had received the assigned treatment and then underwent the opposite treatment for immediate technical or early clinical failure. Overall, 21 patients underwent more than two attempts at revascularization during the first 12 weeks after randomization. As the rate of first attempted revascularization leveled off by the end of week 8 after randomization, all subsequent BTR analyses are presented using this 8 week cutoff.

Table III provides further details of all first and subsequent attempts at revascularization during the first 8 weeks after randomization by randomized group, and the short-term outcome of those attempted revascularizations and the patient status of amputation or death at 8 weeks. Surgery was attempted as a first revascularization procedure ≤8 weeks of randomization in 185 patients. BSX in 171 patients was immediately technically successful and no further attempt at revascularization was undertaken during the 8 weeks after randomization or ≤30 days, whichever was the longest. By 8 weeks, however, 12 of these 171 patients had died and 4 had undergone major amputation of the operated-on leg. BSX in three patients was judged an immediate technical failure, one patient had no further revascularization during the 8 weeks after randomization or ≤30 days, and two patients had further surgery during this time period; one required an amputation within the 8-week/30-day period. Eight patients had BSX as a first revascularization that was judged to be an immediate technical success but went on to have BAP (7 patients) or further surgery (1 patient) during the 8 weeks after randomization or ≤30 days. Two patients had BSX combined with BAP as a technically successful first and only revascularization during the first 8 weeks. Procedures and outcomes in the 224 patients who underwent BAP as the first attempted revascularization ≤8 weeks of randomization can be gleaned from Table III in the same way.

Table I. All surgical and interventional procedures done on the trial leg at any time during follow-up (range, 3-7 years)

Procedures	*All (n = 452)*	*Randomization group*	
		BAP (n = 224)	*BSX (n = 228)*
Revascularization (interventional)			
BAP[a]	299	243	56
BAP of graft stenosis	31	8	23
Stent	9	7	2
Revascularization (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
Débridement	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

BAP, Balloon angioplasty; *BSX*, bypass surgery.
[a]Excludes 2 cases where patient taken to the angiography suite but the procedure was not attempted.
[b]Excludes 4 cases where patient taken to the operating theater but the procedure was not attempted.

Overall, in the first 8 weeks after randomization, patients randomized to BAP were more likely to have their assigned treatment first (208 of 224 [93%] vs 182 of 228 [80%]; $P = .01$, χ^2 test) while those randomized to BSX were more likely to have the opposite treatment first (16 of 228 [7.0%] vs 3 of 224 [1.3%]; $P = .04$, Fisher exact test) or no revascularization (30 of 228 [13.1%] vs 13 of 224 [5.8%]; $P = .01$, Fisher exact test). The number of patients assigned to BAP who did not receive their randomized allocation as the first treatment was too small to make comparisons with those that did. However, those that were assigned to BSX and who did and did not receive surgery as their first treatment were not different in terms of the five baseline characteristics of age, below knee Bollinger angiogram score, presence of tissue loss, serum creatinine, num-

Table II. Cumulative treatments received ≤12 weeks after randomization[a]

	By end of week from randomization											
	Randomized to BAP (n = 224)						*Randomized to BSX (n = 228)*					
Treatment	*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
Randomized treatment only, immediate technical success[b]	104	116	135	148	152	153	111	147	168	170	171	174
Randomized treatment attempted and not done or immediate technical failure[b]	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
Randomized then opposite treatment, including immediate technical failures	7	19	24	28	31	35	1	1	2	2	2	2
More than two revascularization 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; *BSF,* bypass surgery.

[a]As expected, the cumulative number of interventions increases gradually during the time period in both arms. However, the rate of new interventions levels off by week 8 after randomization. For this reason, all subsequent analyses have examined amputation-free survival and overall survival by treatment(s) received ≤8 weeks after randomization.

[b]Immediate technical success as judged by the responsible consultant surgeon or interventional radiologist.

Table III. Revascularizations undertaken ≤8 weeks after randomization by first intervention attempted and randomized group

First attempted revascularization	*All attempted revascularizations and outcomes*[b]	*Patient randomized to*[a]		*Total*
		BAP (n = 224)	*BSX (n = 228)*	
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		2	2
	BSX, BAP		4	4
	BSX, failed BAP		2	2
	BSX, failed BAP, BAP		1	1
	BSX, BSX		1 (D1)	1
	Failed BSX, nil else		1	1
	Failed BSX, BSX		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]Numbers in brackets give the status at 8 weeks from randomization: *A* is alive with trial leg amputated at transtibial level or above; *D* is dead.

[b]Outcomes in first 8 weeks after randomization: *failed* denotes immediate technical failure; *nil else* denotes immediate technical success and no further revascularization procedure ≤8 weeks after randomization or ≤30 days of the first revascularization. Where other revascularizations are listed, these followed the first revascularization ≤8 weeks after randomization or ≤30 days.

bers of ankle pressures obtainable, that best predict the subsequent overall survival of the BASIL trial cohort as a whole.[7] A reason why the assigned BSX was not carried out was recorded for 24 patients: death before surgery/became unfit for BSX (13), no suitable vein (2), and patient refused (9).

Patients who had BAP as their first attempted revascularization 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 revascularization procedure ≤8 weeks after randomization or 30 days, which ever was the

longest) (60 of 224 [27%]) than those who had BSX as a first completed revascularization procedure during the first 8 weeks after randomization (14 of 185 [7.0%]; $P < .001$ χ^2 test). In 42 of 60 (70%) patients, a failed first attempt at BAP was followed by a further intervention and in 39 of 42 (93%) patients that was surgery (37 BSX). Those patients that had successful and unsuccessful first attempted BAP could not be distinguished by baseline characteristics that predicated overall survival.[6,7]

Comparison of outcomes by treatment received in first 8 week after randomization. As described above, because the rate of first attempted revascularization leveled off by the end of week 8 after randomization (Table II), the treatments received up to that point were used to define "on-treatment" groups. Specifically, patients were divided into five groups by treatment(s) received in first 8 weeks after randomization as follows:

1. Group 1: successful surgery only (n = 173)
2. Group 2: successful BAP only (n = 162)
3. Group 3: unsuccessful surgery, defined as immediate technical failure or further intervention within the first 8 weeks or within 30 days of the procedure (n = 11)
4. Group 4: unsuccessful BAP, defined as immediate technical failure or further intervention within 8 weeks or 30 days (n = 60)
5. Group 5: no intervention in first 8 weeks (n = 46)

Surgery groups (1 and 3). Four patients in group 1 and one patient in group 3 underwent endarterectomy and vein patch rather than BSX (n = 179). Details of the BSX in group 1 (n = 169) and group 3 (n = 10) are given in Table IV. Most BSX originated at the common femoral artery. For the distal anastomosis, grafts were divided approximately equally between the above knee popliteal, below knee popliteal, and crural arteries. With regard to the 56 infrapopliteal BSX, 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 wholly or as a composite graft, with or without a vein cuff. More than 90% of the vein BSX were fashioned predominantly with ipsilateral great saphenous vein.[2] Because the number of unsuccessful BSX is small, it is not possible to make any meaningful comparison between those BSX that were successful and those that were not.

BAP groups (2 and 4). Describing often complex attempts at BAP for severe multilevel disease in patients with SLI is more difficult than describing BSX. We have chosen to describe the BAP performed 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 159 of 224 patients (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 4) separate disease lengths (Table V). The numbers of reported transluminal (n = 85) and subintimal (n = 97) BAP were approximately equal, with about 15% BAP being reported as mixed. The pattern and extent of anatomic segments treated was also complex (Table VI). As expected, most patients underwent treatment of the SFA (n = 177) alone (n = 68) or in combination with the popliteal artery (n = 74) and (one or more) crural arteries (n = 32). Most of the remaining patients underwent treatment of the popliteal segments alone or in combination with crural arteries; the number of isolated crural artery BAP was small. Despite the larger number of unsuccessful BAP, as with the surgery groups, it does not appear possible to easily distinguish successful and unsuc-

Table IV. Anatomic extent and type of bypass surgery *(BSX)* in 179 patients undergoing a completed bypass as their first attempted revascularization ≤8 weeks after randomization (on treatment groups 1 and 3)

Bypass extent and type	*Group 1 (n = 169) Successful BSX* No.	*Group 3 (n = 10) Unsuccessful BSX*[a] No.	*All BSX (n = 179)* No.
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
Middle third	3	0	3
Distal third	8	1	9
Anterior tibial artery			
Proximal third	5	1	6
Middle third	5	1	6
Distal third	7	1	8
Peroneal artery			
Proximal third	5	1	6
Middle third	7	0	7
Distal third	4	1	5
Dorsalis Pedis	2	0	2
Tibioperoneal trunk	1	0	1
Dual popliteal and pedal	1	0	1
Conduit type			
Vein	127	9	136
Prosthetic with cuff[b]	28	1	29
Prosthetic no cuff[b]	24	0	24

[a]Unsuccessful BSX means immediate technical failure or further intervention ≤8 weeks of randomisation or 30 days, whichever was longer.
[b]Prosthetic grafts includes composite grafts.

Table V. Number of disease lengths treated and type by balloon angioplasty *(BAP)* in 222 patients undergoing attempted BAP as their first attempted revascularization ≤8 weeks after randomization (on treatment groups 2 and 4)

Variable	*Group 2 (n = 162) Successful BAP only No. (%)*	*Group 4 (n = 60) Unsuccessful BAP[a] No. (%)*
Disease lengths treated, No.		
1	115 (71)	44 (73)
2	26 (16)	14 (24)
3	19 (12)	2 (3)
4	2 (1)	. . .
Type of BAP		
Transluminal	70 (43)	22 (37)
Subintimal	74 (46)	31 (52)
Mixed	18 (11)	7 (11)

[a]Unsuccessful BAP means immediate technical failure or further intervention ≤8 weeks of randomization or 30 days, whichever was longer.

cessful BAP in terms of the numbers of disease lengths treated, the type of BAP, or the anatomic segments treated. Table VII reports the subsequent treatments undertaken by the patients with failed primary procedures (groups 3 and 4).

AFS and OS for these 5 on-treatment groups are shown in Fig 1. AFS (P = .003, log-rank test) but not OS was significantly worse in those patients who had a failed BAP (group 4) than in those who had an initially successful BAP (group 2). Neither AFS nor OS was significantly worse after failed surgery (group 3 vs group 1); however, with only 11 failed cases, this comparison has very low power to detect any difference. None of the other differences between groups were significant. Those with no interventions in the first 8 weeks had slightly poorer AFS and OS initially but their long-term survival was somewhat better than those who were treated successfully.

Vein versus prosthetic BSX. 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 BSX. Patients receiving successful vein BSX as their first and only treatment in the first 8 weeks after randomization (group 1a) had better AFS (P = .003, log-rank test) but not OS (P = .38, log-rank test) than those receiving successful prosthetic bypasses as their first and only treatment in the first 8 weeks (group 1b; Fig 2). There was no significant association between the use of prosthetic material for bypass and any of the baseline clinical data.[7]

Transluminal vs subintimal BAP. 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 BAP. There were no differences in AFS or OS between transluminal and subintimal angioplasty (Fig 3).

Results of BSX after failed BAP. Fig 4 compares AFS and OS in patients who underwent BSX (whether initially technically and/or clinically successful or not) after failed BAP with all patients who underwent BSX (again whether initially successful or not). The 37 patients in group 4 who underwent BSX after first attempted failed angioplasty had a poorer AFS (P = .006, log-ank test) and a somewhat poorer OS (P = .06, log-rank test) than the 184 patients in groups 1 and 3 who underwent BSX as their first treatment.

DISCUSSION

The aim of the BASIL trial was to determine whether, in patients with SLI due to infra-inguinal arterial disease, a BSX first or a BAP first revascularization strategy was associated with a better outcome in AFS, OS, HRQOL, and use of hospital resources.

An ITT of randomized BASIL data showed there was no significant difference between the two trial arms in AFS or OS when the follow-up period was considered as a whole.[2] However, because of the changing relative hazards of surgery and angioplasty over time, patients who survived for 2 years and who were initially randomized to BSX gained a significant 7 months of additional life and an additional nonsignificant 6 months of amputation-free life over the subsequent follow-up period from 2 years to 7 years 9 months after randomization.[3]

The purpose of the current analysis is to describe the nature and timing of first, crossover, and reinterventions received and the resulting AFS and OS. We also wished to compare vein with prosthetic BSX and transluminal with subintimal BAP and examine outcomes from BSX after failed BAP.

Limitations of BTR analyses. BTR analyses of RCT data must be undertaken and interpreted with great caution, and we have quite deliberately presented these in an article separate from the ITT analysis.[3] It is important to appreciate that the validity of the conclusions and recommendations that can be drawn from a preplanned ITT statistical analysis of the randomized data from BASIL is very much greater than that which can be drawn from the present post hoc BTR analysis. With respect to BTR, bias is unavoidable as a result of having lost the protection randomization offers against such error.

Nevertheless, such analyses of the BASIL trial 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 and suggest further areas for research.

Such analyses are especially difficult to undertake in patients that often have complex clinical journeys and multiple comorbidities, and where reintervention and crossover intervention are common, especially in the period following soon after randomization. Investigators have had to make some decisions and assumptions to present what is often a 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

Table VI. Anatomic segments treated in 222 patients undergoing attempted balloon angioplasty *(BAP)* as their first attempted revascularization ≤8 weeks after randomization (on treatment groups 2 and 4)

Anatomic segments treated	*Group 2 (n = 162) Successful BAP No. (%)*	*Group 4 (n = 60) Unsuccessful BAP No. (%)*	*Total No.*
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
Sub-total	8 (5%)	5 (8%)	13
Crural arteries only			
PerA only	1	0	1
ATA + PTA	1	0	1
Sub-total	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.

Table VII. Further treatments after a failed primary procedure (groups 3 and 4) ≤8 weeks from randomization or 30 days after the primary intervention

Next treatment	*Group 3 (n = 11) Unsuccessful BSX No.*	*Group 4 (n = 60) Unsuccessful BAP No.*	*Total No.*
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 (over) speculation. We recognize this analysis could have been done in many different ways and not everyone would have chosen to do it as we have done.

Timing of interventions: comparing strategies not only procedures. Although almost all of the patients randomized in BASIL underwent an attempt at their allocated treatment fairly soon after randomization, 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 revascularization at all.

It is important to re-emphasize that BASIL was not a simple direct comparison of BAP vs BSX. Rather, it was a comparison of a BSX-first with a BAP-first revascularization 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 treatment 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 BAP-first strategy appears to be that the patient is generally likely to be revascularized more quickly. This may be because getting the patient to the interventional suite for a 1-hour procedure and then back to the main ward is logistically much easier than getting them to an operating theatre for a 2 to 3 hour procedure and then back to a critical care bed. Or, it may be

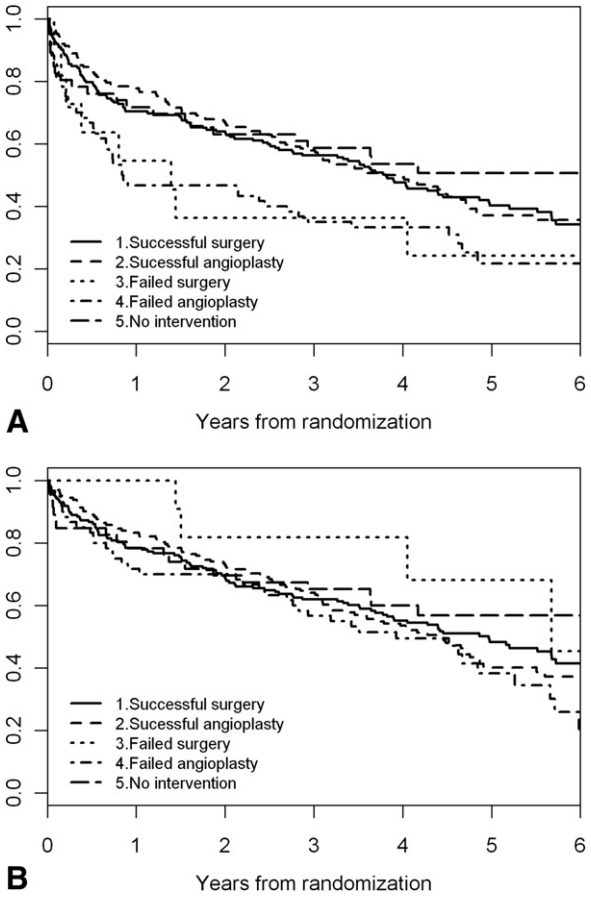

Fig 1. A, Amputation-free survival and **(B)** overall survival for the five treatment groups during follow-up.

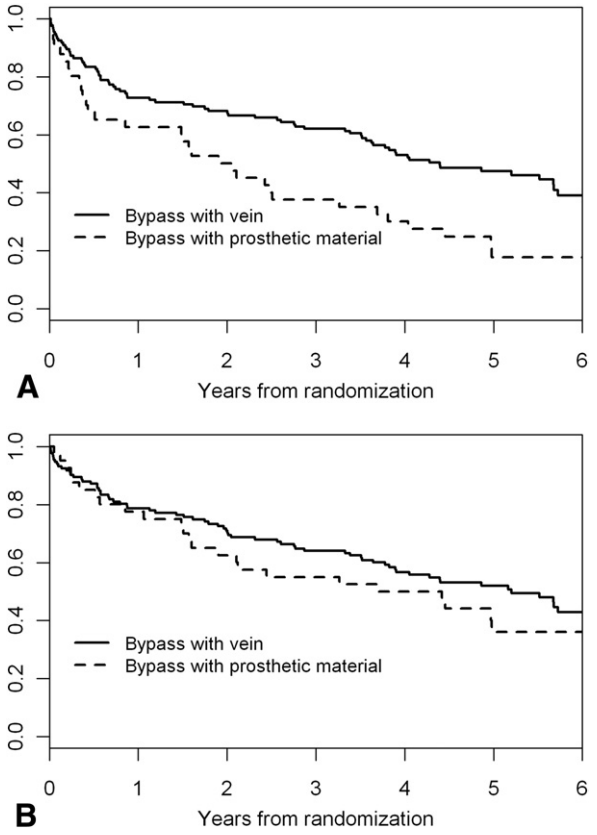

Fig 2. A, Amputation free survival and **(B)** overall survival for patients undergoing bypass surgery according to type of bypass conduit.

that patients going forward for BAP are perceived to need less workup than those destined for BSX.

With regard to events after the index procedure, we expected BAP to be associated with a significant immediate and early failure rate in this patient group, and we anticipated that a proportion of those patients would require further, often surgical, procedures.[8] With respect to surgery, it was reasonable to expect the early failure rate would be lower but that reinterventions, either angioplasty or further open surgery, might be deemed necessary to maintain graft patency. These factors have to be offset against the higher morbidity associated with BSX.[2]

By comparing strategies, we have been able to compare not just individual index procedures but also a range of other factors, some clinically driven and some logistical, that in reality impact the complex journeys these patients navigate before and after the first attempted revascularization. Observational uncontrolled studies are not sensitive to these sorts of important real-world influences; in reality, they are difficult to perceive and quantify without the confines of a RCT.

A small number of randomized patients were not revascularized either by BAP or, BSX. These patients exhibited an initially poor survival but subsequently appeared to fare as well as those undergoing revascularization. This is probably because the non-revascularized cohort comprised two quite different groups of patients. First, there were those who became too ill to undergo (or died before) surgery; and, second, there were those whose symptoms improved with best medical and nursing care to a point where they were no longer deemed to require revascularization (or the patients themselves withdrew consent). Two patients were not operated on because the surgeon could not find a suitable vein for bypass before surgery.

These data are in keeping with others who reported surprisingly good outcomes with best medical and nursing care alone even in patients with unreconstructable CLI.[9] Physicians looking after this group of patients will recognize that randomizing them to BSX or BAP, and then ensuring that they undergo the assigned intervention in a timely manner, requires a great deal of time spent with the patient and the family. It is a great credit to the teams in each of the 27 hospitals that about 70% of those invited to take part in the trial accepted the offer; and that almost all of them received their allocated treatment within a few weeks.

High rates of early BAP failure. Although patients were likely to receive BAP more quickly, the rate of imme-

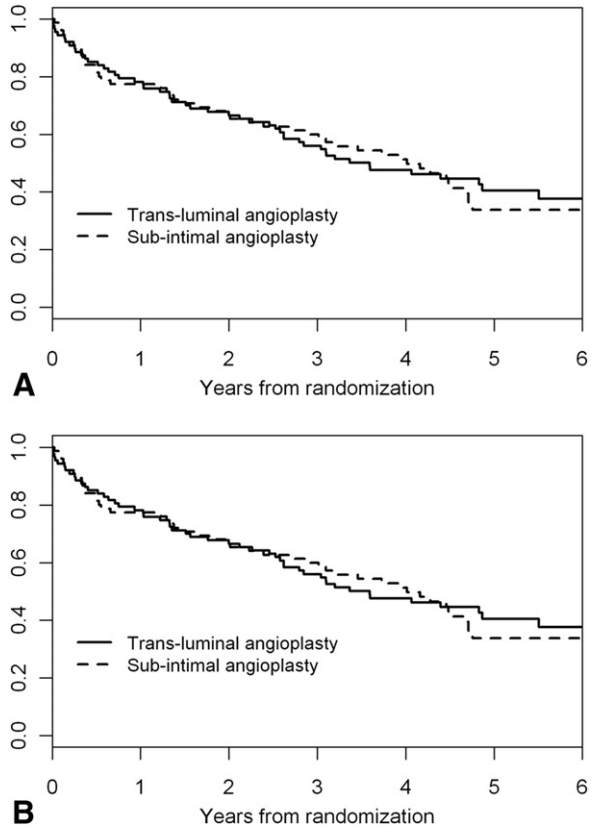

Fig 3. A, Amputation free survival and **(B)** overall survival for patients undergoing transluminal and subintimal angioplasty.

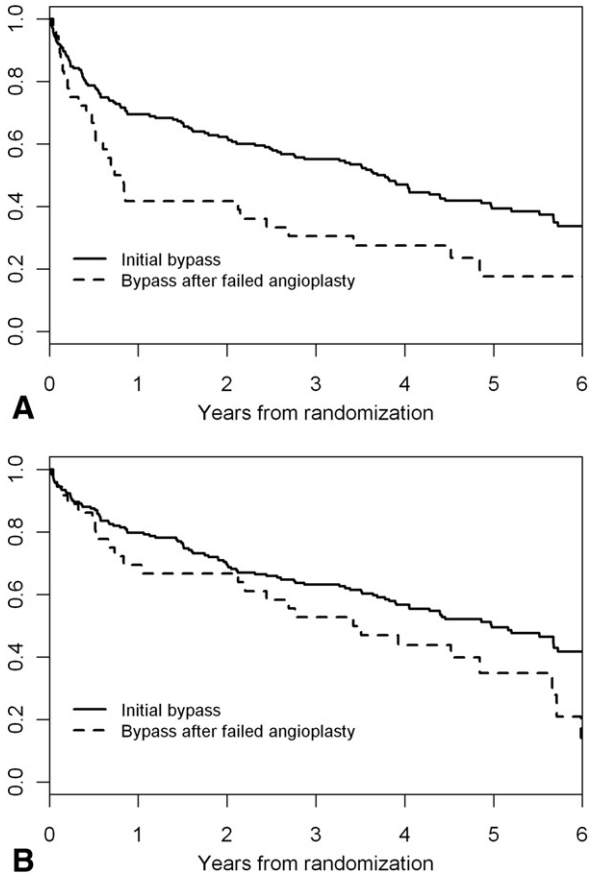

Fig 4. A, Amputation free survival and **(B)** overall survival in patients randomized to and undergoing bypass surgery and in patients undergoing bypass surgery after failed balloon angioplasty.

diate technical and early clinical failures after BAP was significantly higher than after BSX. As was to be expected, most patients undergoing BAP within BASIL had severe, multilevel disease.[6] A review of the literature concerning similar patients, not those with claudication and relatively discrete disease, indicates that the BASIL data on immediate and early BAP failure are by no means atypical.[10,11] Interventionalists will be keen to understand if there are any factors that can be used to predict immediate and early BAP failure in this patient group. Data on the perceived reasons for immediate technical failure, as characterized by the responsible interventionalist, are available and analyses of these data in relation to clinical and angiographic patterns of disease[5,6] are on-going. However, present data show no clear difference between successful and unsuccessful BAP in extent, location, and type of BAP performed.

Results of BSX after failed BAP. It is often said, although on the basis of little real evidence, that an unsuccessful BAP does not jeopardize the chances of subsequent BSX.[12] In other words, apart from perhaps the cost, there is "nothing to lose" by at least trying BAP first: if it works, then all well and good, and if not, then proceed to BSX.[13] Notwithstanding all the caveats surrounding BTR analyses, the BASIL trial data do not appear to support this "free shot" view of BAP.

Patients with immediate or early BAP failure did significantly worse in terms of AFS even though most later had apparently, at least initially, successful BSX. This may be because failed BAP simply identifies a group of patients who are going to do badly regardless of what surgical or endovascular treatment is offered.[7] Alternatively, it may be that a failed BAP in some way jeopardizes the chances of subsequent successful BSX in the longer term because it affects the type and extent of BSX required or the run-off, or both. By looking at the perceived causes of BAP failure, comparing the characteristics of BSX undertaken as first procedure with BSX undertaken after failed BAP, 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 on-going and will be the subject of a further report in due course. For now, however, we can say that about one-quarter of BAP for SLI are likely to fail immediately (technically) or ≤8 weeks (clinically) and that, for reasons as yet unclear, such patients will tend to do badly even if they subsequently undergo an apparently initially successful BSX.

Stenting and BAP. Some have suggested that the current standard of care for SLI involves routine or "bail out" stenting. Further, it has been suggested that if the trial had been conducted in an era/health economy where interventionalists had access to and chose to use modern peripheral, possibly drug-eluting,[14-20] stent (graft) technology, then results of the BASIL trial would have been very different. There is no way of knowing whether this is true. All we can really say with confidence is that the costs of the interventional treatment would be much greater than they were in BASIL where very few stents were placed. However, a careful review of the most recently published literature leads us to conclude that stenting (stent grafting) may confer some benefit above the inguinal ligament and in claudicant patients with limited disease of the superficial femoral artery[15,16,21,22] but that current evidence lends little support to the idea that stenting in SLI patients with extensive multilevel infrainguinal disease is likely to meaningfully improve the overall clinical effectiveness above that achieved by angioplasty alone.[23]

Looking at the BAP data presented here it is difficult for us to believe that current stenting (stent graft) technology would have materially improved overall outcomes in the BAP arm of the trial. However, we are aware that others may take a different view and that this is a rapidly developing field[24] with new data on pharmacologic[25,26] and procedural adjuvant techniques[27] regularly entering the public domain.[28,29] Furthermore, going forward it is likely that vascular specialists will increasingly want to exploit the synergies to be enjoyed by combining surgical and endovascular procedures in the same leg.[30]

Prosthetic bypass. The BASIL trial investigators have been criticized for allowing the admission of prosthetic bypasses and the trial participants for failing to be sufficiently aggressive in using nonsaphenous venous conduit. However, a review of the recent literature reveals a conflicting view of the role of prosthetic bypass for this condition. 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,[31-34] but prosthetic grafts are still being widely promoted, and one presumes used, for patients with SLI/CLI.[35,36] Various design modifications such as heparin bonding[37] and distal precuffing[36,38] are claimed to be effective in increasing graft patency to acceptable levels, even for tibial bypasses.[39,40] Others take the view that vein should be used at all costs and that even high-risk nonsaphenous, spliced venous conduit is always preferable to a prosthetic reconstruction.[35,41]

With regard to the BASIL trial, after considerable discussion and debate among the investigators and the participants, the randomization was allowed 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):

1. Femorodistal bypass using a prosthetic conduit, usually with a venous cuff or boot below the knee, was a common operation.
2. Vein bypass using nonsaphenous conduit was a less common operation.
3. Preoperative vein mapping was not universally available or used, and as a result, many patients would probably have been randomized only to become a protocol violation when the surgeon elected to use prosthetic rather than poor quality or nonsaphenous vein during the surgery.

For these reasons, trial organizers strongly believed that a vein bypass-only trial would be unable to recruit. A three-way trial of BAP vs vein vs prosthetic BSX was briefly mooted but quickly discounted for clinical, logistical, and statistical reasons.

In the event, about one-quarter of the BSX undertaken in the BASIL trial was constructed with prosthetic material (either in whole or in part) and >90% of vein BSX were predominantly constructed with ipsilateral great saphenous vein.

Although nonrandomized, BTR analyses have to be interpreted with great caution because of the risk of bias, it does appear that in patients undergoing initially successful BSX in the first 8 weeks after randomization, prosthetic BSX performed very much less well in AFS, and to a lesser extent OS, than vein BSX or (transluminal or subintimal) angioplasty. There was no significant association between the use of prosthetic material vs vein for bypass and any of the predictive baseline clinical variables.[7] So, this lack of durability does not appear to be obviously due to the selection for prosthetic bypass of higher-risk patients within the group randomized to surgery; rather it appears to result solely from a lack (in the opinion of the responsible surgeon) of suitable vein. So, although not randomized, we believe the data offer reasonably convincing evidence for the superiority of vein (predominantly saphenous) BSX and, importantly, also BAP over prosthetic BSX in this patient group.

Although one has to be very cautious when conflating ITT[2,3] and BTR analyses, we believe the overall BASIL trial recommendation that patients likely to live >2 years after intervention should usually have BSX rather than BAP should be viewed in the context of the available bypass conduit. Thus, it seems at least possible that had only those patients able to undergo vein BSX been randomized in BASIL, then the longer-term advantages of BSX over BAP in terms of AFS, and possibly OS, would have been substantially greater than those actually observed because of the inclusion within BASIL of a significant number of generally very poorly performing prosthetic bypasses in the BSX arm. It is also seems likely that many of the patients who could not undergo a vein BSX would have been better served by an attempt at BAP, where possible, rather than prosthetic bypass in the first instance (even if their predicted survival was >2 years). The BASIL trial data reaffirms once again that surgeons should make every effort to use vein and to view prosthetic material in such patients as a last resort; probably after BAP.

Choice of end points. AFS and OS were chosen as the main clinical end points for BASIL because they are unam-

biguous and of clear clinical significance. During the last 10 years, there has been much discussion of end point selection and a trend towards using rather "softer," nonclinical (surrogate), composite end points. Several articles have urged caution in the interpretation of such end points, which can be manipulated to give the appearance of clinical efficacy when none exists.[23,42] The issue of end point selection is considered at length elsewhere;[3] suffice to say, having presented the ITT analysis in terms of AFS and OS, we think it is appropriate to restrict our BTR analysis to those end points in this report.

AFS and OS after BSX and BAP are influenced by comorbidity and not just the effectiveness of the revascularization, and this makes applying the rigor of randomization so powerful and important. The patients in the two arms of the BASIL trial were not different in any clinically important respect; as such, one can reasonably conclude that any differences in outcome observed between the two groups are the result of the two different strategies used. Regrettably, and perhaps somewhat remarkably, the BASIL trial remains the only RCT of surgical vs endovascular treatment of infrainguinal disease for limb-threatening ischemia.

Commentators on BASIL have also questioned the wisdom of using OS as a major end point because limb revascularization is not intended to improve long-term survival. The prognosis of OS in patients with dysvascular amputation is very poor. We think that by preserving the limb, we also usefully extend life, although it would take an RCT that randomizes to revascularization or primary amputation to know that for sure.

Some physicians have expressed surprise that we did not use patency as major end point. This issue was discussed at some length when the trial was designed in 1997 and 1998 and we actively decided not to use patency as an end point for a number of clinical, scientific, and logistical reasons; specifically:

First, patients are not concerned with patency but with symptom relief (pain, wound healing), limb salvage and preservation of life; we determined these should be the primary end points.

Second, there is an imperfect relationship between patency and these clinically important end points in these patients. Some patients experienced failure of their intervention but no further reinterventions were required or undertaken. Particularly in the group with rest pain only (especially those with ankle pressures >50 mm Hg) BAP, even BSX, may function as a temporary bypass buying time for the leg/patient while collaterals develop. So lives and legs can be lost with patent grafts/endovascular procedures, while patients/legs not infrequently often remain intact and pain-free after the intervention has "failed" hemodynamically.

Third, assessing the patency of complex multisegment BAP for multilevel disease in SLI patients in a standard and reproducible manner is very difficult, perhaps impossible, especially across 27 centers.

However, because AFS does not per se measure the "quality" of revascularization, we collected measures of HRQOL,[3,4] hemodynamic data (ankle pressures), and information on relief of rest pain and healing of wounds and minor amputations. These latter data are currently being analyzed and will be the subject of a further separate report.

It has been suggested that we further analyze the data using "amputation-and-reintervention-free" survival because reintervention is an important clinical event for the patient and this composite end point might provide more complete picture than AFS alone.

As discussed above, BTR analyses of RCTs are fraught with methodologic challenges, especially when dealing with patients that are subject to so many reinterventions and crossover interventions. We have given very considerable thought about how to do this in a way that is sensible, transparent, and clinically useful. We accept, however, that regardless of how we choose to do this, our methods will not find favor with everyone and that no method is perfect. We have already explained why we chose to use AFS and OS. With regard to reintervention, we have already described both quantitatively and qualitatively the risks and nature of re-interventions following both strategies in this and other papers.[2,3]

The problem with using the suggested "amputation-and-reintervention-free" survival is that it only accounts for the first reintervention (which may not be the clinically significant one). Also, some reinterventions are discretionary, being based on hemodynamic and/or duplex ultrasound data rather than symptoms. For these reasons, we have chosen to restrict our analyses to AFS and OS at this stage, although we may choose to report the trial according to different end points in due course.

Nonstandard follow-up protocols and graft surveillance. The trial has been criticized because it did not mandate a specific postintervention follow-up regimen, which it has been suggested should, at least for the bypass grafts, have included routine duplex ultrasound-based surveillance.

Once again, the BASIL trial must be viewed in the context of what was considered usual practice in 1997 and 1998 when the trial was designed. At that time, at least in the UK, duplex-based graft surveillance was not universally used; indeed, not all surgeons are yet to be convinced that it improves clinically important outcomes. The Vein Graft Surveillance Randomized Trial (VGST), the RCT available, concluded "intensive surveillance with duplex scanning did not show any additional benefit in terms of limb salvage rates for patients undergoing vein bypass graft operations, but it did incur additional costs." [43] So although there is a lot of expert opinion in support of routine duplex ultrasound-based vein graft surveillance,[44] we are not aware of any level I evidence that it is clinically effective or cost-effective. As stated above, graft surveillance is an issue we are currently exploring through on-going analyses in respect of the BASIL trial, and we will report on that in due course in a further manuscript.

CONCLUSIONS

Although much has been said and written about the relative merits of BSX and BAP in the treatment of SLI,[11,18,45-48] before BASIL, there was a complete absence of level I evidence from RCTs in the field. Like all RCTs, BASIL is imperfect, but nevertheless, the investigators and participants believe it represents a useful compass pointing the way toward evidence-based practice.[49]

Taking together (cautiously) the previous ITT[2,3] and the current BTR analyses, the overall recommendation from BASIL is that SLI patients predicted to live >2 years, and with a useable vein, should usually have BSX first. This is because the long-term results of saphenous vein BSX are good, the rate of BAP failure is high, and results of BSX after failed BAP are significantly worse than for primary BSX. However, patients expected to live <2 years, and those without a useable vein, should usually have BAP first because they will not survive to reap the longer-term benefits of surgery and the results of prosthetic BSX are poor.

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.

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APPENDIX

BASIL trial Participants and Contributors

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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.

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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.

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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

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