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Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Health-related quality of life outcomes, resource utilization, and cost-effectiveness analysis

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Background: The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial showed that survival in patients with severe lower limb ischemia (rest pain, tissue loss) who survived postintervention for >2 years after initial randomization to bypass surgery (BSX) vs balloon angioplasty (BAP) was associated with an improvement in subsequent amputation-free and overall survival of about 6 and 7 months, respectively. We now compare the effect on hospital costs and health-related quality of life (HRQOL) of the BSX-first and BAP-first revascularization strategies using a within-trial cost-effectiveness analysis.

Methods: We measured HRQOL using the Vascular Quality of Life Questionnaire (VascuQol), the Short Form 36 (SF-36), and the EuroQol (EQ-5D) health outcome measure up to 3 years from randomization. Hospital use was measured and valued using United Kingdom National Health Service hospital costs over 3 years. Analysis was by intention-to-treat. Incremental cost-effectiveness ratios were estimated for cost per quality-adjusted life-year (QALY) gained. Uncertainty was assessed using nonparametric bootstrapping of incremental costs and incremental effects.

Results: No significant differences in HRQOL emerged when the two treatment strategies were compared. During the first year from randomization, the mean cost of inpatient hospital treatment in patients allocated to BSX ($34,378) was estimated to be about $8469 (95% confidence interval, $2,417-$14,522) greater than that of patients allocated to BAP ($25,909). Owing to increased costs subsequently incurred by the BAP patients, this difference decreased at the end of follow-up to $5521 ($45,322 for BSX vs $39,801 for BAP) and was no longer significant. The incremental cost-effectiveness ratio of a BSX-first strategy was $184,492 per QALY gained. The probability that BSX was more cost-effective than BAP was relatively low given the similar distributions in HRQOL, survival, and hospital costs.

Conclusions: Adopting a BSX-first strategy for patients with severe limb ischemia does result in a modest increase in hospital costs, with a small positive but insignificant gain in disease-specific and generic HRQOL. However, the real-world choice between BSX-first and BAP-first revascularization strategies for severe limb ischemia due to infrainguinal disease cannot depend on costs alone and will require a more comprehensive consideration of individual patient preferences conditioned by expectations of survival and other health outcomes. (J Vasc Surg 2010;51:43S-51S.)

Severe leg ischemia (SLI), characterized by rest/night pain and tissue loss due to ulceration or gangrene, leads to significant morbidity and mortality and also to the consumption of considerable health and social care resources in developed and developing countries. The absence of level 1 evidence from randomized controlled trials (RCTs) has led to continuing debate and disagreement about the best treatment for such patients.[1]

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 (BAP)-first revascularization strategy for SLI caused by infrainguinal disease.

When the entire follow-up period was considered, there was no significant difference in amputation-free survival (AFS) or overall survival (OS) between the two treatments. However, for those patients surviving 2 years from randomization, a BSX-first revascularization strategy was associated with a reduced hazard ratio of 0.85 (95% confi-

dence interval [CI] 0.5-1.07; $P = .108$) for subsequent AFS and of 0.61 (95% CI, 0.50-0.75; $P = .009$) for subsequent OS 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 OS 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).[2,3]

Although AFS was the primary trial end point, other important consequences of the chosen revascularization strategy included the effect on hospital costs and the patients' perceptions of their health-related quality of life (HRQOL). We integrated the prospective definition and measurement of these secondary end points into the design of the BASIL trial to allow a more comprehensive consideration of the primary factors that might influence the choice between BSX-first and BAP-first revascularization strategies.

METHODS

The BASIL trial is registered with the National Research Register (NRR) and as an International Standard Randomized Controlled Trial, number ISRCTN 45398889 (http://www.controlled-trials.com/ISRCTN45398889/45398889).

The methods of the BASIL trial have been reported previously.[2,3] The BASIL trial design integrated measurement of survival, AFS, HRQOL, and the use of hospital inpatient services. These trial outcomes allowed consideration of the primary health and resource consequences after the two different revascularization strategies. Individual patient hospital costs were collected to the end of follow-up. All analyses were by intention-to-treat using the perspective of the individual patient for HRQOL and the UK hospital sector for resource use.

Health-related quality of life. We measured HRQOL using the Vascular Quality of Life Questionnaire (VascuQol),[4] the generic Short Form 36 (SF-36) health survey,[5] and utility scores based on the EuroQoL 5-D (EQ-5D).[6] Higher scores on the VascuQol, SF-36 scales and summary scores, and EQ-5D indicate better health and well-being as perceived by the patient. These measures were collected using a self-administered protocol at baseline (randomization) and at 3, 6, 12, 24, and 36 months after randomization. All patients were asked to provide HRQOL data out to 3 years from randomization, whether or not they had undergone major amputation of the trial leg.

The VascuQol is a disease-specific questionnaire designed to assess specific elements of HRQOL for individuals with lower limb ischemia. It includes 25 items (questions) subdivided into five domains: pain (4 questions), symptoms (4 questions), activities (8 questions), social (2 questions), and emotional (7 questions). Each question has a 7-point response scale ranging from 1 (worst possible) to 7 (best possible). Responses were averaged for individual

domain and composite total scores, giving equal weight to each question and domain.

The SF-36 contains 36 questions that measure HRQOL across eight domains: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health (general mood or affect including anxiety, depression and psychological well-being), energy/vitality, bodily pain, and general health perceptions. For each dimension, question responses were coded, scored, and transformed into a scale from 0 (worst possible score) to 100 (best possible score). The SF-36 items were combined into physical and mental component summary scores using recommended procedures.[7]

The SF-6D, a single-index preference-based measure, was also derived from the SF-36 responses using the Brazier algorithm.[8] This provided a further summary measure of the SF-36 items using a health state valuation model that complements the EQ-5D. Because it is based on the broader and more detailed SF-36 items and has a strong theoretic and methodologic basis, the SF-6D enabled us to consider whether the level of and change in patient perceptions of well-being after randomization was similar across these two leading preference-based measures of well-being.

The $EQ-5D_{index}$ covers five dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has three levels (no problem, some problem, or extreme problem), and participants are asked to indicate the level that corresponds to their current level of function or experience on each dimension. The EQ-5D responses were converted into a single weighted utility (preference-based) score using the original time trade-off tariff set.[9] This is a standard and well-established set of preference weights used in clinical and economic evaluations based on experimental, observational, and modeling studies using UK populations. Overall self-rated health status was also collected using the visual analog scale (EQ-VAS) scores ranging from 0 (worst health) to 100 (best health).

Calculation of quality-adjusted life-years. Quality-adjusted life-years (QALYs) were calculated per patient over 3 years using the $EQ-5D_{index}$. A standard multiplicative model was used to estimate QALYs by the area under linear interpolation of the $EQ-5D_{index}$ trajectory for each individual using the intervals in months 0 to 3, 3 to 6, 6 to 12, 12 to 24, and 24 to 36. These utility-adjusted survival time intervals were summed to generate a total QALY score for each patient. Although we did measure survival >3 years (all patients were monitored for minimum of 3 years and 54% for 5 years) and did collect some HRQOL data for a longer time horizon, we chose not to estimate QALYs >3 years from randomization due to the incomplete clinical follow-up coupled with an increase in the proportion of HRQOL nonresponders.

Missing data due to attrition. We expected that attrition over time would occur as the horizon for follow-up increased and that missing scores would become more prevalent as trial participants died (informative dropout) or failed to complete questionnaires (nonresponse).

Table I. Vascular Quality of Life questionnaire domain and overall scores by intention-to-treat analysis at different time points from randomization to angioplasty or bypass surgery[a]

Health domain	Baseline, mean (SD)		3 mon, mean (SD)		12 mon, mean (SD)		36 mon, mean (SD)	
	Angioplasty (n = 214)	*Surgery (n = 204)*	*Angioplasty (n = 161)*	*Surgery (n = 153)*	*Angioplasty (n = 132)*	*Surgery (n = 121)*	*Angioplasty (n = 46)*	*Surgery (n = 49)*
Activity	2.33 (0.98)	2.45 (1.07)	3.65 (1.56)	3.87 (1.49)	3.79 (1.57)	3.93 (1.55)	3.85 (1.65)	3.71 (1.72)
Symptoms	3.63 (1.42)	3.73 (1.40)	5.11 (1.22)	5.33 (1.16)	5.28 (1.18)	5.35 (1.27)	5.43 (1.13)	5.16 (1.23)
Pain	2.34 (1.21)	2.48 (1.30)	4.50 (1.73)	4.72 (1.68)	4.65 (1.72)	4.84 (1.73)	4.78 (1.50)	4.58 (1.73)
Social	2.83 (1.58)	3.08 (1.82)	4.16 (2.03)	4.45 (1.83)	4.43 (1.95)	4.64 (1.77)	4.33 (1.85)	4.20 (2.08)
Emotional	3.06 (1.33)	3.13 (1.45)	4.58 (1.60)	4.80 (1.54)	4.90 (1.68)	5.06 (1.54)	5.00 (1.63)	4.86 (1.79)
Overall	2.79 (1.01)	2.90 (1.10)	4.32 (1.39)	4.55 (1.30)	4.53 (1.42)	4.67 (1.37)	4.61 (1.41)	4.44 (1.55)

[a]Does not include four patients lost to follow-up.

After adjusting for data unavailable because of death, the overall rate of missing HRQOL data was 32%. We report analyses using both complete information (case-wise deletion of observations when HRQOL scores were missing) and information based on imputation of missing EQ-5D data adjusted for informative dropout. We used an imputation method for missing values, using all available information after multivariate imputation by chained equations[10,11] for missing $EQ\text{-}5D_{index}$ scores that were used in the QALY analysis.

Inpatient hospital use and cost. Resource use data were collected after randomization on the index intervention and all subsequent interventions, hospital stays, and hospital clinic visits. Patient-specific hospital use was measured using the overall duration of stay for each hospital inpatient episode and the number of day and outpatient visits. Acute hospital inpatient days were disaggregated by surgical and medical specialty (eg, vascular surgery, high-dependency unit, intensive care unit, cardiology, general medicine, rehabilitation) based on the reasons for admission and recorded interventions and procedures. Hospital activity data were recorded in all participating centers for each patient. Cumulative hospital episodes, days, and visits were restricted to 3 years from the date of randomization.

These measures of hospital resource use were converted into cost estimates using National Health Service (NHS) hospital costs derived routinely for Scotland, a region of the UK that accounted for 142 of 452 randomized patients (31%) in the trial. The inpatient days, broken down by specialty, were valued using the average specialty-specific cost per day obtained from the Scottish system of hospital cost statistics.[12] Day and outpatient visits were costed on a per diem/attendance basis.

All procedures (surgical, radiologic, and amputations) were measured using patient-specific anesthetic, operating theater, and recovery suite times; the number and grades of medical, nursing, and theater staff; and the specific procedure-related equipment and consumables. Staff time was valued using UK national pay scales. Purchase costs were used to value the typical mix of equipment and consumables used in the surgical and radiologic procedures.

Hospital use and procedure costs were calculated on a price base of financial year 2006/2007 in UK pounds (£). Costs were converted to US dollars ($) using the 2006 purchasing power parity (PPP) rate of currency conversion ($/£ PPP = 0.64). A discount rate of 3.5% recommended by Her Majesty's Treasury was used to calculate the present value of annual costs incurred over 3 years from the date of randomization. We discounted health effects at 3.5% following current guidance from the National Institute for Clinical Excellence (NICE)[13] suggesting that both costs and health effects should be discounted using a uniform rate.

Statistical analysis. Data analysis was performed using Stata 10 software (StataCorp, College Station, Tex).[14] Descriptive statistics were based on completed baseline and follow-up HRQOL questionnaires for complete cases with no missing items. Analysis of the $EQ\text{-}5D_{index}$ was performed using a generalized estimating equation model to adjust for correlated scores measured over time. Imputations for missing $EQ\text{-}5D_{index}$ scores were generated using an algorithm for creating models for imputation (Stata packages pred_eq and check_eq and the Stata ice package).[14] Summary statistics for costs are based on all patients, with no allowance for right-censored cases. We report marginal costs (differences in cumulative costs over 3 years) using an ordinary least squares estimator. Given the anticipated skewness (a heavy right-hand tail) of the length of stay and cost data, we also used generalized median regression estimators that are more robust with respect to outliers with extremely high cost profiles.

Effectiveness was measured using mean differences in AFS (the primary end point of the trial), mean differences in OS, and patient-specific total QALYs to 3 years based on the EQ-5D. Incremental cost-effectiveness ratios were estimated using the mean difference in hospital cost and the mean difference in effectiveness between the BAP and BSX groups. To capture the uncertainty surrounding the estimate of mean differences in costs and effects, we used scatter plots of incremental costs and effects and a 90% confidence ellipse based on a nonparametric bootstrap technique calculated using 1000 resamples of the difference

Table II. Unadjusted Short Form-36 domain scores by intention-to-treat analysis at different time points from randomization to angioplasty or bypass surgery[a]

	Baseline, mean (SD)		3 mon, mean (SD)	
SF-36 domains	Angioplasty (n = 212)	Surgery (n = 204)	Angioplasty (n = 162)	Surgery (n = 152)
Physical functioning	22.69 (19.39)	23.04 (19.91)	30.77 (25.44)	32.43 (26.55)
Social functioning	40.63 (28.36)	44.24 (31.37)	55.32 (31.58)	57.81 (30.92)
Role physical	10.26 (25.49)	13.11 (28.99)	25.46 (38.56)	23.03 (36.00)
Role emotional	31.45 (42.77)	36.27 (44.29)	51.65 (45.21)	49.78 (45.07)
Mental health	58.87 (22.73)	60.08 (21.42)	65.93 (19.84)	68.55 (20.38)
Energy/vitality	34.15 (20.78)	36.32 (20.81)	42.28 (24.21)	44.61 (23.48)
Bodily pain	30.40 (21.68)	31.97 (22.90)	55.21 (27.92)	57.31 (27.96)
General health	49.14 (19.81)	48.04 (21.51)	50.06 (20.67)	52.37 (22.22)

[a]Does not include four patients lost to follow-up.

Table III. EuroQol and Short Form-6D scores by intention-to-treat analysis at different time points from randomization to angioplasty or bypass surgery[a]

	Baseline, mean (SD)		3 mon, mean (SD)		12 mon, mean (SD)		36 mon, mean (SD)	
Variable	Angioplasty (n = 214)	Surgery (n = 203)	Angioplasty (n = 162)	Surgery (n = 152)	Angioplasty (n = 132)	Surgery (n = 119)	Angioplasty (n = 48)	Surgery (n = 49)
EQ-5D	0.26 (0.32)	0.28 (0.34)	0.53 (0.31)	0.57 (0.28)	0.56 (0.31)	0.62 (0.28)	0.61 (0.25)	0.54 (0.35)
EQ VAS	0.53 (0.21)	0.55 (0.21)	0.60 (0.20)	0.62 (0.19)	0.60 (0.20)	0.64 (0.19)	0.63 (0.21)	0.61 (0.19)
SF-6D	0.53 (0.10)	0.54 (0.11)	0.60 (0.13)	0.61 (0.13)	0.63 (0.13)	0.63 (0.12)	0.64 (0.14)	0.60 (0.15)

EQ-5D, EuroQol weighted index score; *EQ VAS,* visual analog scale; *SF-6D,* Short Form weighted index score.
[a]Does not include four patients lost to follow-up.

in cost and effects drawn with replacement from the original sample of patients.

RESULTS

The VascuQol. The disease-specific VascuQol provides evidence that BSX and BAP both have a positive effect on all domains affected by SLI (Table I).[15] Although patients allocated to BSX reported slightly better scores at baseline, the overall pattern was very similar over time and between groups. Most of the improvement occurred ≤3 months of randomization, with very little change thereafter. This sustained positive effect, particularly in the pain and symptom domains, was maintained over time.

SF-36 health domains and summary scores. SF-36 domains and summary scores are reported in Table II. Scores before randomization, based on 213 of 224 responders (95%) in the BAP group and on 207 of 228 responders (91%) in the BSX group, were very similar in the two trial arms. BASIL patients perceived their health to be much lower than that reported in general populations matched for age and gender and in patients undergoing endovascular or conventional aortic aneurysm repair.[16] Large floor effects (proportion of patients in the worst possible health states) were observed for the role physical (82%) and role emotional (61%) scales. With the exception of role emotional (29%), ceiling effects (proportion of patients in the best possible heath state) were small and well below 10% for most scales. Patients in both treatment groups reported improved SF-36 domain and summary

scores by 3 months, but little further improvement was recorded. Most of the gains in SF-36 were concentrated in the scales that capture perceptions of physical well-being. However, there was also slight improvement over a longer time period in the SF-36 mental health domain.

EuroQol (EQ-5D). This general pattern of improvement was also reflected in the EuroQol and SF-6D weighted index scores (Table III). Although there was weak evidence that utility scores might be somewhat better in the BSX group, patients in both treatment groups reported virtually identical levels and trajectories in the EQ-5D over time. Scores were improved at 3 months and sustained to 3 years without significant differences between the BSX-first and BAP-first groups. A similar pattern was recorded for EQ VAS scores and utility scores based on the SF-6D, suggesting a high degree of concordance among these alternative measures of self-reported well-being.

Effect of EQ-5D informative dropout and nonresponse. Patient death (informative dropout) and patient failure to respond at one or more time intervals (nonresponse) accounted for missing HRQOL data. Patients who died were given an EQ-5D score of 0 to allow for informative dropout. The response rates for those eligible were 93%, 77%, 70%, 44%, and 35%, respectively, at baseline, 3 months, and at 1, 2, and 3 years after randomization, giving an overall response rate of 68%. Response rates were similar in the two trial arms, and the pattern of missing information was virtually identical across the other HRQOL questionnaires.

Table II. Continued

| 12 mon, mean (SD)		36 mon, mean (SD)	
Angioplasty (n = 132)	*Surgery (n = 119)*	*Angioplasty (n = 48)*	*Surgery (n = 49)*
33.60 (24.51)	37.39 (29.21)	35.10 (27.76)	31.94 (30.05)
59.85 (26.63)	61.97 (29.85)	61.98 (27.53)	56.12 (36.10)
30.11 (39.41)	31.51 (38.85)	26.56 (42.65)	25.51 (39.36)
52.02 (45.17)	58.82 (42.23)	55.56 (47.31)	46.94 (46.61)
68.67 (21.41)	70.52 (18.85)	70.33 (20.71)	67.18 (20.22)
41.21 (23.88)	47.56 (21.62)	44.79 (24.28)	44.59 (25.14)
54.29 (25.78)	60.04 (27.53)	56.94 (25.07)	55.10 (31.51)
48.96 (21.79)	50.76 (20.01)	48.21 (18.46)	46.51 (21.34)
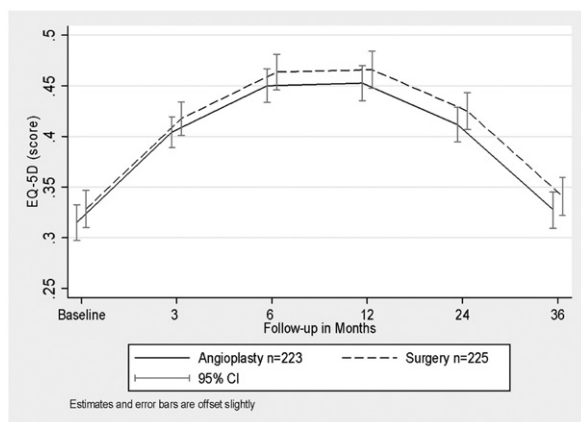
Fig 1. EuroQol-5D scores, up to 36 months after randomization at baseline, are based on multiple imputation of missing information. *CI*, Confidence interval.

Up until 1 year, very small differences (<0.04) in mean EQ-5D scores were detected when the distribution of EQ-5D was assessed using a base case, allowing for informative dropout only, and an alternative based on informative dropout and multiple imputation for missing data for nonresponders. At 2 and 3 years, the mean imputed EQ-5D scores were about 0.10 higher compared against scores allowing only for informative dropout. This would be expected given the higher proportion of zeros (or deaths) in the more restricted analysis that only allowed for informative dropout (ie, complete cases and deaths).

EQ-5D–imputed scores were also consistently lower for individuals who underwent an amputation ≤3 years of randomization. Although closely matched at baseline, EQ-5D imputed scores by 3 months were 0.06 lower in the amputee group. This difference remained very steady throughout the follow-up period.

The generalized estimating equation analysis showed that EQ-5D–imputed scores were better for up to 3 years in the BSX-first group (Fig 1). This small but statistically insignificant advantage in favor of BSX was also detected when the analysis was restricted to patients with complete data or informative missing data.

Hospital admissions, length of stay, and cost. The use of inpatient hospital services over time was broadly similar for patients in both trial arms, as measured by the number of hospital admissions and total days in the hospital. Over 3 years, both groups had an average of three hospital stays, and the average length of stay, cumulated over all inpatient admissions, was just >2 months. During the first year from randomization, length of stay was shorter in the BAP-first group, with a mean (interquartile range) of 37 days (4-46 days) vs 45 days (12-60 days) for BSX-first. In years 2 to 3, the difference in hospital stay shifted in favor of BSX because the BAP patients used a further 20 days vs 15 days in the BSX. By 3 years, there was only a small (3 days) and insignificant difference in the mean (interquartile range) length of hospital stay between the two groups, with 57 days (8-73 days) for BAP vs 60 days (16-82 days) for BSX. Given the additional short-term morbidity of BSX, there was less of a difference between the two groups than might perhaps have been expected.

These data, however, encompassed all hospital admissions, not just those directly related to the index admission. Patients randomized to BAP had a significantly higher immediate failure and reintervention rate, plus there are a range of medical and social factors, other than the status of the trial leg and its treatment, that determine admission and length of stay in hospital.

Inpatient episodes primarily occurred in ward settings with relatively little use of the more specialized services provided in high dependency units (HDU) and intensive therapy units (ITU). Patients randomized to a BSX-first strategy used an average of about half a day more of HDU than did BAP-first patients. There was a slight difference in ITU use, with a few additional hours used by the BSX-first patients. The main cost driver remained the number and duration of episodes in acute ward settings. After 3 years' follow-up, operating room/angiography suite costs accounted for 9% of total hospital costs in the BAP-first group; as expected, the corresponding figure was higher, at 14%, for the BSX-first group. Most of the operating room/angiography suite and hospital ward costs occurred in the first year after randomization.

Table IV. Difference in cumulative total costs of a surgery-first compared with angioplasty-first strategy

		Estimation method	
Cumulative costs	Least squares	Robust regression	Median regression
During 1 yr of follow-up	$8469[a] ($2434 - $14,505)	$8699[b] ($6042 - $11,356)	$9744[b] ($4914 - $14,574)
During 3 yrs of follow-up	$5521 ($−2929 - $13,971)	$9132[b] ($4832 - $13,433)	$11507[a] ($3792 - $19,222)
No.	448	448	448

Marginal effects (95% confidence intervals). Positive effects reflect the additional costs of a surgery-first strategy. Least squares and robust regression estimates report the difference in mean cumulative costs. Median regression estimates are based on differences in median cumulative costs.
[a]$P < .01$.
[b]$P < .001$.

During the first year from randomization, the estimated mean cost of inpatient hospital treatment in patients randomized to BSX was $34,378 ($28,701 hospital stay and $5677 procedure costs), which was approximately one-third higher than the $25,909 ($22,605 hospital stay and $3305 procedure costs) for patients randomized to BAP. This difference in mean total hospital and procedures costs of about $8469 was significant (95% CI, $2434-$14,505) at 1 year. However, owing to increased costs incurred by the BAP patients, this difference in total hospital and procedures costs at the end of 3 years decreased to $5521 ($45,322 BSX vs $39,801 BAP) and was no longer significant.

The distribution of costs in both groups was also skewed with a long, right-hand tail. Costs were >$175,000 in 10 patients (7 in the BAP group, 3 in the BSX group). Table IV reports the marginal effect on total cumulative cost when more robust estimation methods were used. Adjusting for outliers using generalized median regression had an important effect when costs were analyzed during 3 years of follow-up because less weight was given to patients with extremely high costs, many of whom were in the BAP-first group. This had the effect of increasing the estimated cost differences to $9132, which was much closer to the estimated difference in median costs of $11,507.

AFS, OS, and quality-adjusted survival. As reported elsewhere, there was little difference in AFS or OS between the two groups when the follow-up period was taken as a whole.[2,3] Up to 3 years, the difference in mean AFS was 12 days (95% CI, −89-64 days), and the difference in mean OS was 32 days (95% CI, −100-37 days). These small differences in restricted mean AFS and OS, when calculated over 3 years, favored the BAP group but were not significant.

When combined with patient-specific EQ-5D scores, these absolute differences in survival led to virtually no difference in the number of quality-adjusted life (days) between the two trial arms. The small positive differences in HRQOL in favor of BSX, as measured by EQ-5D$_{index}$ when combined with absolute survival in the two groups out to 36 months from randomization, generated a mean quality-adjusted lifetime of 412 days for BAP and 423 days for BSX. The mean difference of 11 days (95% CI, −42-64 days), or just 0.03 of a QALY, failed to achieve conventional levels of significance.
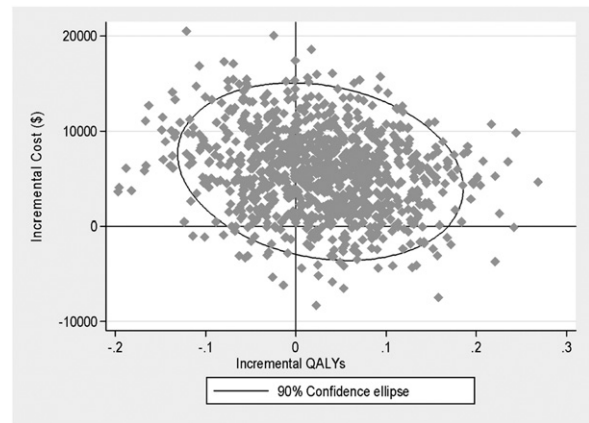

Fig 2. Joint density of incremental cost and incremental quality adjusted life-year (QALY) of surgery compared with angioplasty. Positive (negative) incremental costs show that surgery is more (less) costly than angioplasty. Positive (negative) incremental QALYs show that surgery is more (less) effective than angioplasty.

Cost-effectiveness. Incremental cost-effectiveness ratios (ICER) are calculated as the ratio of the difference in costs between BSX-first and BAP-first strategies to the difference in effects. However, when the difference in effects were measured using AFS and OS up to 3 years after randomization, the ICERs were not only negative but were also estimated with a great degree of imprecision because the small differences were centered close to zero. The ICER point estimate can be estimated with the ratio of the additional costs of BSX-first strategy to the difference in QALYs to generate a cost-per QALY of $184,492 ($5521/ 0.03). Using the more robust estimates of the difference in costs reported in Table IV would increase the ICER to $304,400 ($9132/0.03).

The bootstrapped joint densities of the difference in cost (BSX − BAP) between the two trial arms and the difference in QALYs (BSX − BAP) out to 3 years are shown in Fig 2. About half of the distribution (58%) is located in the upper right quadrant of the graph (more costly and more effective). A further 33% is located in the upper left quadrant (more costly and less effective), with 7% in the lower right quadrant (less costly and more effective) and 2%

in the lower left quadrant (less costly and less effective). A 90% confidence ellipse superimposed on this joint distribution encompassed the upper left quadrant, suggesting that additional costs of a BSX-first strategy could lead to a slight decrease in QALYs.

DISCUSSION

As expected, the disease-specific and generic HRQOL of the BASIL trial cohort was very low at baseline.[17-21] No significant differences between the two trial arms emerged across a range of generic and disease-specific HRQOL measures.[22] Although patients had a very low HRQOL before treatment, BSX and BAP both had very similar effects on short-term gains in HRQOL that were sustained for at least 3 years after randomization. This plateau effect probably reflects the fact that the aggregate data are conflating two very different groups: patients who keep their legs[23] and those who do not.[24-27] As others have found,[28,29] the relative clinical and hemodynamic advantages and disadvantages of a BSX-first vs a BAP-first strategy for managing SLI due to infrainguinal disease do not seem easily distinguishable by means of disease-specific or generic HRQOL.[30]

These results should be interpreted with caution, because data were missing in about one-third of the patients eligible to report HRQOL trial end points. Up to 12 months, however, data completeness in BASIL was actually above that reported in the Project of Ex-Vivo Vein Graft Engineering via Transfection (PREVENT) III clinical trial, which measured QOL using VascuQol.[31] Response rates for BASIL compared with PREVENT III reveal a similar pattern of attrition due to nonresponse over time of 93.3% vs 92.3% at baseline, 76.0% vs 65.7% at 3 months, and 68.0% vs 62.5% at 12 months. Beyond 12 months, response rates were equally low in both trial arms; this is disappointing but perhaps to be expected given the clinical realities for these high-risk patients with a range of comorbidities.[32-34] Responders were more likely to have an intact trial leg and, presumably therefore, to exhibit higher levels of generic but especially disease-specific HRQOL.[35-41] Like PREVENT III, nonresponse was associated with amputation, and this limited the information available to measure the effects of the alternative management strategies on HRQOL in this patient subgroup.

The hospital costs during the first year were approximately one-third higher with a BSX-first than with a BAP-first strategy. Although the cost of the BSX procedure itself is significantly greater than that of BAP, the main difference in costs between the two strategies is related to the length of hospital stay, including the greater requirement for patients undergoing BSX to be cared for within an HDU or ITU environment. We were unable to quantify the use and associated costs of health and social services outside the hospital or costs beyond 3 years related to further interventions arising from SLI. Thus, our results underestimate some elements of the costs of managing SLI[42-44] that arise from the rehabilitation of amputees. However, the number of major limb amputations was similar in the two trial arms,

so it is reasonable to assume that these additional costs would also have been roughly the same after BSX and BAP.

The resource costs estimated in this pragmatic vascular surgery trial accounted for inpatient hospital stay(s) after randomization up to 3 years. It reflected contemporary utilization of hospital inpatient services by patients allocated to one of the strategies in BASIL. Although we believe our estimate of the differences in hospital costs between these alternative policies is robust, the absolute and relative differences are primarily a reflection of observed practice in the BASIL trial centers between 1999 and 2007 and the specific resource unit costs applied in our study. The use of hospital resources and cumulative costs during year 1 are also broadly similar to recent reports that consider the distribution of costs over a longer time horizon.[42,43] When costs are measured in a more comprehensive way, capturing not only the initial episode of care but also subsequent readmissions for (often) multiple operations and procedures, a more accurate estimate of the resource consequences of caring for patients presenting with SLI is obtained. Our results are based on the expected use of resources within a UK NHS context with corresponding levels of pay and prices that may not be easily generalizable to other health care systems. Costs may also change over time as novel and possibly more effective interventions are adopted and a new pattern of service use is established.

Our findings should be interpreted carefully against the background of comparisons of resource use for a relatively small number of patients who present with SLI, undergo diagnostic imaging, and are selected for some form of revascularization. This has the inevitable effect of making inferences that are less precise and reliable than we would like because BASIL was powered to detect differences in the primary end points of AFS and OS for a selected population.

In addition to the challenges of distributions estimated with a (large) degree of imprecision, we have the attendant problem of censoring for those patients still alive at 3 years whose future QOL and resource utilization was not observed. These estimates are based on HRQOL and absolute mortality over 3 years. We know that the balance of risks and benefits for BSX vs BAP changes significantly after 2 years for some patients, and this will not be captured completely by this analysis. Thus, it is possible that longer-term survival gains might translate into positive differences in quality-adjusted survival in favor of BSX. However, this inference is limited because the numbers of patients available for longer-term analysis is very small and we do not have HRQOL data beyond 3 years.

CONCLUSIONS

This HRQOL and economic evaluation of BSX-first and BAP-first revascularization strategies in patients presenting with SLI due to infrainguinal disease can be used to inform some of the arguments surrounding the relative advantages and disadvantages of each intervention. BSX does appear to have a significant effect on the distribution

of hospital costs and to be associated with positive health effects in some patients. However, when the additional cost of BSX is compared against the small increase in survival adjusted for HRQOL, the cost per QALY is relatively high. As such, there remains a substantial possibility that for some patients, BSX may lead to an increase in costs with little and possibly negative effects on health measured in the short to medium term. Further studies of the effect of targeted BSX or BAP for patients facing different survival chances might identify more efficient use of resources, if less invasive and less costly interventions are directed towards those who may not live long enough to benefit from the apparent survival advantages conferred by a BSX-first strategy.

However, the real-world choice between BSX-first and BAP-first revascularization strategies for SLI due to infrainguinal disease cannot depend upon a consideration of costs alone. A more comprehensive consideration of individual patient preferences conditioned by expectations of survival and other health outcomes will be required.[45]

AUTHOR CONTRIBUTIONS

Conception and design: JF, DA, JB, FF, IG, GR, CR, AB
Analysis and interpretation: JF, DA, JB, FF, IG, GR, CR, AB
Data collection: JF, DA, JB, AB
Writing the article: JF, AB
Critical revision of the article: JF, DA, JB, FF, IG, GR, CR, AB
Final approval of the article: JF, DA, JB, FF, IG, GR, CR, AB
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