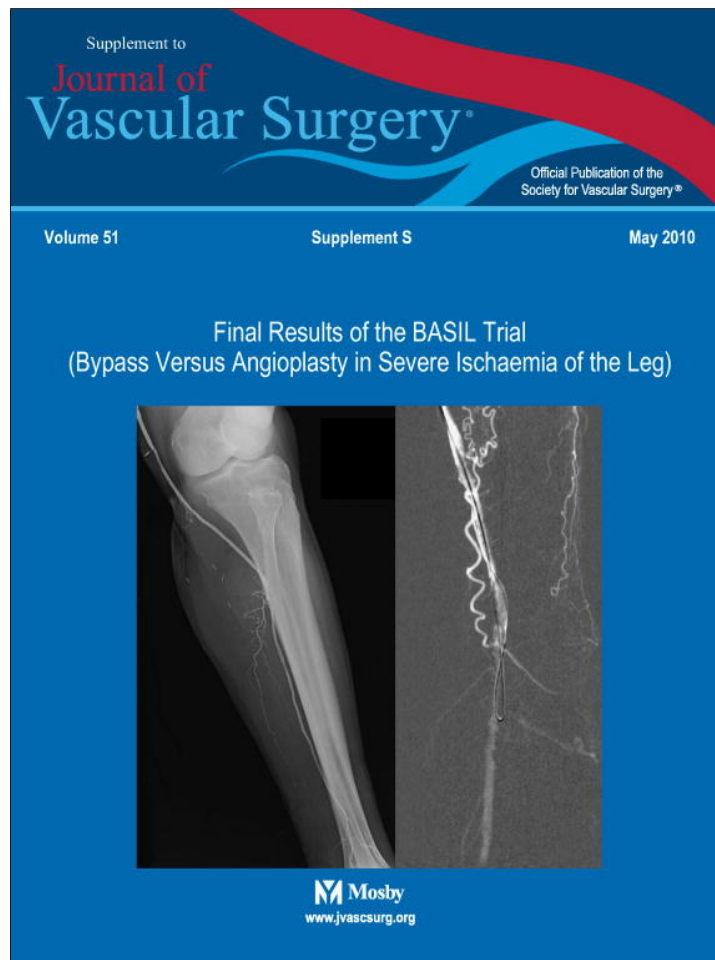


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Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: A survival prediction model to facilitate clinical decision making

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Background: An intention-to-treat analysis of the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial showed that in patients with severe lower limb ischemia (SLI) due to infrainguinal disease who survived for 2 years after intervention, initial randomization to a bypass surgery (BSX)-first vs balloon angioplasty (BAP)-first revascularization strategy was associated with improvements in subsequent overall survival (OS) and amputation-free survival (AFS) of about 7 and 6 months, respectively. This study explored the value of baseline factors to estimate the likelihood of survival to 2 years for the trial cohort (Cox model) and for individual BASIL trial patients (Weibull model) as an aid to clinical decision making.

Methods: Of 452 patients presenting to 27 United Kingdom hospitals, 228 were randomly assigned to a BSX-first and 224 to a BAP-first revascularization strategy. Patients were monitored for at least 3 years. Baseline factors affecting the survival of the entire cohort were examined with a multivariate Cox model. The chances of survival at 1 and 2 years for patients with given baseline characteristics were estimated with a Weibull parametric model.

Results: At the end of follow-up, 172 patients (38%) were alive without major limb amputation of the trial leg, and 202 (45%) were alive. Baseline factors that were significant in the Cox model were BASIL randomization stratification group, below knee Bollinger angiogram score, body mass index, age, diabetes, creatinine level, and smoking status. Using these factors to define five equally sized groups, we identified patients with 2-year survival rates of 50% to 90%. The factors that contributed to the Weibull predictive model were age, presence of tissue loss, serum creatinine, number of ankle pressure measurements detectable, maximum ankle pressure measured, a history of myocardial infarction or angina, a history of stroke or transient ischemia attack, below knee Bollinger angiogram score, body mass index, and smoking status.

Conclusions: Patients in the BASIL trial were at high risk of amputation and death regardless of revascularization strategy. However, baseline factors can be used to stratify those risks. Furthermore, within a parametric Weibull model, certain of these factors can be used to help predict outcomes for individuals. It may thus be possible to define the clinical and anatomic (angiographic) characteristics of SLI patients who are likely—and not likely—to live for >2 years after intervention. Used appropriately in the context of the BASIL trial outcomes, this may aid clinical decision making regarding a BSX- or BAP-first revascularization strategy in SLI patients like those randomized in BASIL. (*J Vasc Surg* 2010;51:52S-68S.)

Severe leg ischemia (SLI), characterized by rest/night pain and tissue loss (ulceration, gangrene), leads to significant morbidity and mortality and to the consumption of considerable health care and social care resources in developed and in developing countries.¹ The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial remains the only multicenter, randomized controlled trial (RCT) to compare a bypass surgery (BSX) first with a balloon angioplasty (BAP) first revascularization strategy in patients with SLI due to infrainguinal disease.

An intention-to-treat analysis of the BASIL trial showed that BSX-first and BAP-first strategies both led to similar amputation-free survival (AFS) and overall survival (OS) out to 2 years from randomization, although BSX had significantly more morbidity and was about one-third more expensive in the short-term.² However, for those patients who survived for >2 years after intervention, initial randomization to a BSX-first strategy was associated with a significant increase of 7.3 months in restricted mean OS and a nonsignificant increase of 5.9 months in restricted

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*The trial participants listed in the Appendix.

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mean AFS during the subsequent follow-up that averaged 3.1 years (range, 1-5.7 years).³ Hospital costs and health-related quality of life (HRQOL) were not significantly between the two groups during the first 3 years.⁴

These data suggest that patients like those randomized in the BASIL trial and who are expected to live >2 years should usually be considered for BSX rather than BAP. Conversely, BASIL-like patients not expected for survive >2 years appear to benefit more from a BAP-first strategy because, in the short-term (≤ 2 years), surgery is significantly more morbid and expensive.

These data and interpretations have been discussed at length among the trial investigators and participants. They have also been presented at meetings to numerous groups of vascular surgeons and interventionalists from many different countries. Many of these clinicians have made it known to the investigators that they would value an analysis of the data that attempts to predict survival for the entire BASIL cohort as well as for individual BASIL patients determined from robust (objective) baseline variables that are easily and widely available in day-to-day clinical practice at the point of clinical decision making with respect to pursuing a BSX-first or BAP-first strategy for their patients.

We agree that given the key clinical messages to emanate from the BASIL trial, it is entirely logical to try to model the factors that might predict whether such patients might survive for 2 years after randomization. However, such modelling is fraught with methodologic and interpretational challenges, and any estimates of survival so produced must be used with great care and in the context of the overall clinical situation for each patient.

Notwithstanding those important caveats, the specific aim of this article is to report the results of a study that examined whether unambiguous, easily obtainable baseline data could be used to make informed judgments about how long a BASIL-like patient is likely to live; and, specifically, how likely the patient is to survive >2 years, which appears to be the point where the relative merits of a BAP-first and BSX-first revascularization strategy change.

METHODS

All patients who participated provided written informed consent, and the study was approved by the Multi-center Research Ethics Committee (MREC) for Scotland. The BASIL trial was registered with the National Research Register (NRR) and the International Standard Randomised Controlled Trials Number (ISRCTN) Scheme (Number 45398889; <http://www.controlled-trials.com/ISRCTN45398889/45398889>).

Overview of trial methods and collection of follow-up (death) data. The BASIL trial methods have been published elsewhere.^{2,3} Briefly, between August 1999 and June 2004, consultant vascular surgeons and interventional radiologists in 27 United Kingdom (UK) hospitals randomized 452 patients to a BSX-first or a BAP-first revascularization strategy. Inclusion criteria were patients who required revascularization because of SLI, defined as rest pain or tissue loss from ulcer or gangrene, or both, of

arterial etiology present for >2 weeks. Patients' diagnostic imaging had to show a pattern of disease that, in the consultants' joint opinion, could equally well be treated by infrainguinal BSX or BAP.

Randomization was stratified by center and then into four groups by clinical presentation of rest pain only vs tissue loss and ankle pressure of ≥ 50 vs < 50 mm Hg; namely, (A) rest pain only, ≥ 50 mm Hg; (B) rest pain only, < 50 mm Hg; (C) tissue loss, ≥ 50 mm Hg; and (D) tissue loss < 50 mm Hg. Preintervention angiograms were scored using the Bollinger method and the Trans-Atlantic Inter-Society Consensus (TASC) II classification system.⁵

Centers were encouraged to undertake the allocated procedure as soon as possible after randomization. The responsible consultant vascular surgeons and interventional radiologists were permitted to use their preferred techniques, equipment, and graft material as for their normal practice.

Details of patients recruited in Scottish centers were logged with the Information and Statistics Division of the National Health Service in Scotland. Data were gathered from interrogation of hospital paper and electronic records and from contacts with general practitioners. In addition, this prospectively gathered information was crosschecked by reviewing all available hospital case notes of trial patients at the end of the study. The status of all patients alive at the end of follow-up was 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.

The clinical end points were major AFS, defined as a patient alive without amputation of the trial leg at transtibial level or higher, and OS. Angiograms were scored according to the Bollinger method (infrainguinal segments) and the TASC II criteria.¹ Details of the angiogram scoring are the subject of a further report.⁵

Statistical analysis. For the survival analyses, patients with no clinical report of survival were taken as censored at end February 2007 if their survival information was from the Information and Statistics Division, at end July 2007 if their death information was from the 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 whose deaths investigators thought were unlikely to have been recorded in the UK were censored at their last follow-up times; all ≤ 1 year 1 month of randomization.

The patient-specific clinical and anatomic (angiographic) variables specified as covariates in the trial protocol were entered into univariate and multivariate analyses with a Cox proportional hazards model using all available follow-up data (range, 3-7 years of follow-up).

To predict how a future patient might behave in terms of overall survival up to 2 years from randomization, a parametric survival model was developed using a regression approach based on the Weibull distribution as imple-

Table I. Number of and total follow-up time to major amputations of trial leg or deaths, or both, from any cause between randomization and 2 years and after 2 years from randomization

| Follow-up period | Patients with amputation of trial leg or death from any cause with trial leg intact, No. | Total years of follow-up to this end point (AFS) | Patients with death from any cause, No. | Total years of follow-up to death (OS) |
|-----------------------------|--|--|---|--|
| Randomization to 2 years | 172 | 658 | 131 | 736 |
| >2 years from randomization | 108 | 734 | 119 | 863 |

AFS, Amputation-free survival; OS, overall survival.

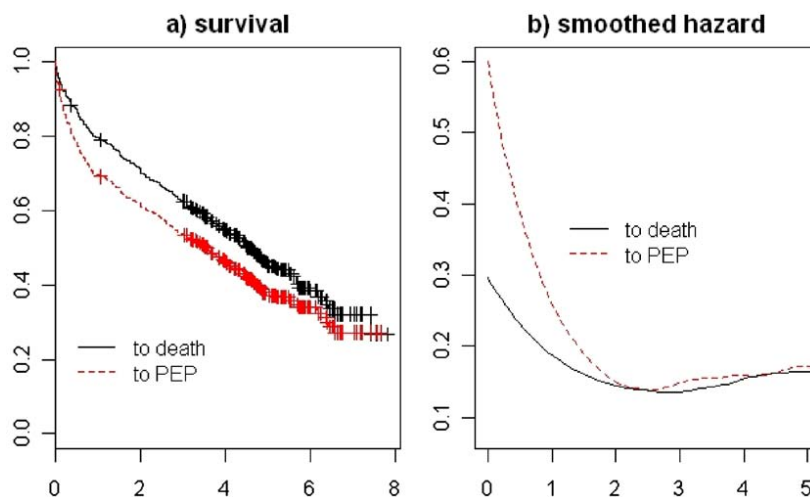


Fig 1. Amputation-free survival, the primary end point (PEP), and overall survival for the BASIL trial cohort are presented as (A) survival curves and (B) as smoothed estimates of the hazard functions for each event. The vertical lines on the survival curve indicate that an observation is censored. The x axis on A and B is time from randomization in years.

mented in the SAS LIFEREG procedure. Only survival up to 2 years from randomization was used, with all survivors beyond this time censored at 2 years.

The regression model used the baseline covariates defined in the protocol to predict survival and also a further set of four measures that were considered likely to affect overall survival. The additional measures were a history of angina or myocardial infarction (MI), history of transient ischemic attack (TIA) or stroke, the number of ankle pressure measurements that could be obtained (range, 0-3), and the maximum ankle pressure obtained as a continuous variable. The latter two variables provided more information on the ankle pressures than the simple dichotomy of ankle pressure higher or lower than 50 mm Hg that was specified in the protocol. The regression model was simplified by dropping certain variables using a combination of backward selection and informed choice, taking note of the plausibility of the directions of the associations in the data.

This approach runs the risk of over-fitting the model, which has the effect of making the predictions more extreme than are justified by the data. To overcome this, the model was developed on a training data set that consisted of a randomly selected 75% of the original data. A shrinkage factor was then calculated that corrects for over-fitting, and

the predictions were validated on the remaining 25% of the data.

A Weibull parametric survival model has a hazard function that can increase or decrease with time from randomization. The model estimates a shape parameter and a linear predictor that together can be used to calculate the predicted survival to a given time for any combination of baseline characteristics. Specifically, the probability of surviving to time t can be written as

$$S(t) = \{-[t \exp(-\eta)]^s\},$$

where s is the shape parameter and η is a linear predictor calculated from the baseline characteristics. A shape parameter of 1.0 gives a model with constant hazard (exponential distribution of survival times), whereas a shape parameter <1.0 indicates a hazard that is decreasing over the follow up period.

RESULTS

Deaths and amputations before and after 2 years.

To place the predictive analyses in context, the numbers of deaths and major amputations of the trial leg (the primary end point for the trial) before and after 2 years from randomization are reported in Table I. Fig 1, A

Table II. Hazard ratios from Cox proportional hazards model of time to death during the first 2 years after randomization

| Variable | No. | Univariate analysis | | Multivariate analysis | |
|---|-----|---------------------|-------|-----------------------|-----|
| | | HR (95% CI) | P | HR (95% CI) | P |
| Randomization stratification group | | | | | |
| Tissue loss, ankle pressure >50 mm Hg (C) | 222 | 2.42 (1.29-4.55) | <.001 | 1.88 (0.98-3.60) | .01 |
| Ankle pressure <50 mm Hg (B & D) | 137 | 3.62 (1.92-6.85) | | 2.56 (1.30-5.04) | |
| No tissue loss, ankle pressure >50 mm Hg (A) | 93 | | | | |
| Serum creatinine (log values), mmol/L | | | | | |
| Low (<4.466) | 148 | 1.61 (0.99-2.62) | .005 | 1.73 (1.05-2.87) | .02 |
| High (>4.7274) | 143 | 2.24 (1.4-3.59) | | 2.01 (1.25-3.25) | |
| Missing | 21 | 1.28 (0.48-3.39) | | 1.79 (0.66-4.9) | |
| Medium (4.466-4.7274) | 140 | | | | |
| Body mass index, kg/m² | | | | | |
| Underweight (<20) | 51 | 1.45 (0.85-2.5) | .065 | 1.47 (0.84-2.58) | .32 |
| Overweight (>25) | 115 | 0.79 (0.49-1.29) | | 0.96 (0.58-1.59) | |
| Obese and severely obese (>30) | 53 | 0.59 (0.29-1.2) | | 0.66 (0.32-1.35) | |
| Missing | 85 | 1.26 (0.78-2.02) | | 1.18 (0.72-1.92) | |
| Desirable range (20-25) | 148 | | | | |
| Diabetic, type 1 and 2 together; yes vs no | 190 | 1.26 (0.88-1.78) | .196 | 1.24 (0.83-1.84) | .28 |
| Age group, y | | | | | |
| 70-79 | 193 | 2.04 (1.28-3.24) | <.001 | 1.6 (0.98-2.6) | .08 |
| ≥80 | 112 | 2.28 (1.38-3.77) | | 1.74 (0.99-3.06) | |
| <70 | 147 | | | | |
| Smoking | | | | | |
| Exsmoker | 199 | 1.47 (0.9-2.4) | .135 | 1.72 (1.03-2.87) | .09 |
| Current smoker | 164 | 1.06 (0.63-1.8) | | 1.5 (0.84-2.68) | |
| Nonsmoker | 89 | | | | |
| Statin | 152 | 0.71 (0.48-1.05) | .081 | 0.8 (0.53-1.21) | .27 |
| Bollinger angiogram score (below knee) | | | | | |
| 5-8 | 131 | 2.12 (1.35-3.34) | .004 | 1.95 (1.21-3.15) | .01 |
| ≥8 | 129 | 1.75 (1.1-2.79) | | 1.7 (1.01-2.85) | |
| Missing | 34 | 1.07 (0.47-2.47) | | | |
| <5 | 158 | | | | |
| Bollinger angiogram score (above knee) | | | | | |
| 5-8 | 165 | 1.55 (0.98-2.47) | .047 | 1.45 (0.88-2.37) | .16 |
| ≥8 | 119 | 1.83 (1.13-2.95) | | 1.6 (0.95-2.72) | |
| Missing | 34 | 0.99 (0.43-2.31) | | | |
| <5 | 134 | | | | |
| TASC group | | | | | |
| C | 186 | 1.03 (0.66-1.63) | .266 | 1.04 (0.63-1.73) | .47 |
| B | 122 | 0.89 (0.54-1.48) | | 1.02 (0.57-1.8) | |
| A best | 12 | 0.23 (0.03-1.76) | | 0.28 (0.03-2.2) | |
| Missing | 39 | 0.66 (0.3-1.47) | | 0.43 (0.05-3.48) | |
| D (worst) | 93 | Base | | | |

CI, Confidence interval; HR, hazard ratio; TASC, TransAtlantic Inter-Society Consensus.

shows AFS (the primary end point) and OS for the whole BASIL trial cohort. After the first 1 to 2 years of follow-up, the two survival curves are fairly parallel, indicating that few new amputations occurred at this length of time from randomization. This is clearer in the smoothed estimates of the hazard functions (Fig 1, B), which shows that amputations in the first 1.5 years increase the primary end point hazard (AFS) compared with that for death only, but few extra amputations occur after that time to increase the hazard of the primary end point (AFS) compared with death. Note also that the initially high hazard declines during the first 2 years and appears to become fairly constant after the first 2 years, or perhaps slightly sooner. This reducing risk is shown by the numbers of amputations during follow-up: 61, 5, 7, 3, and 3 in years 1 to 5, respectively.

Relationship between survival to 2 years and baseline clinical factors (Cox model). The results of the Cox proportional hazard models for death from any cause (OS) during the period up to 2 years from randomization are reported in Table II for the covariates defined in the original trial protocol. Because the baseline variables are correlated, the coefficients change in the multivariate model. The baseline factors that remained significant in the multivariate Cox model were in descending order of their significance in the multivariate model:

- BASIL randomization stratification group
- Below-knee Bollinger angiogram scores⁵
- Body mass index
- Age
- Presence of diabetes (type I and type II together)

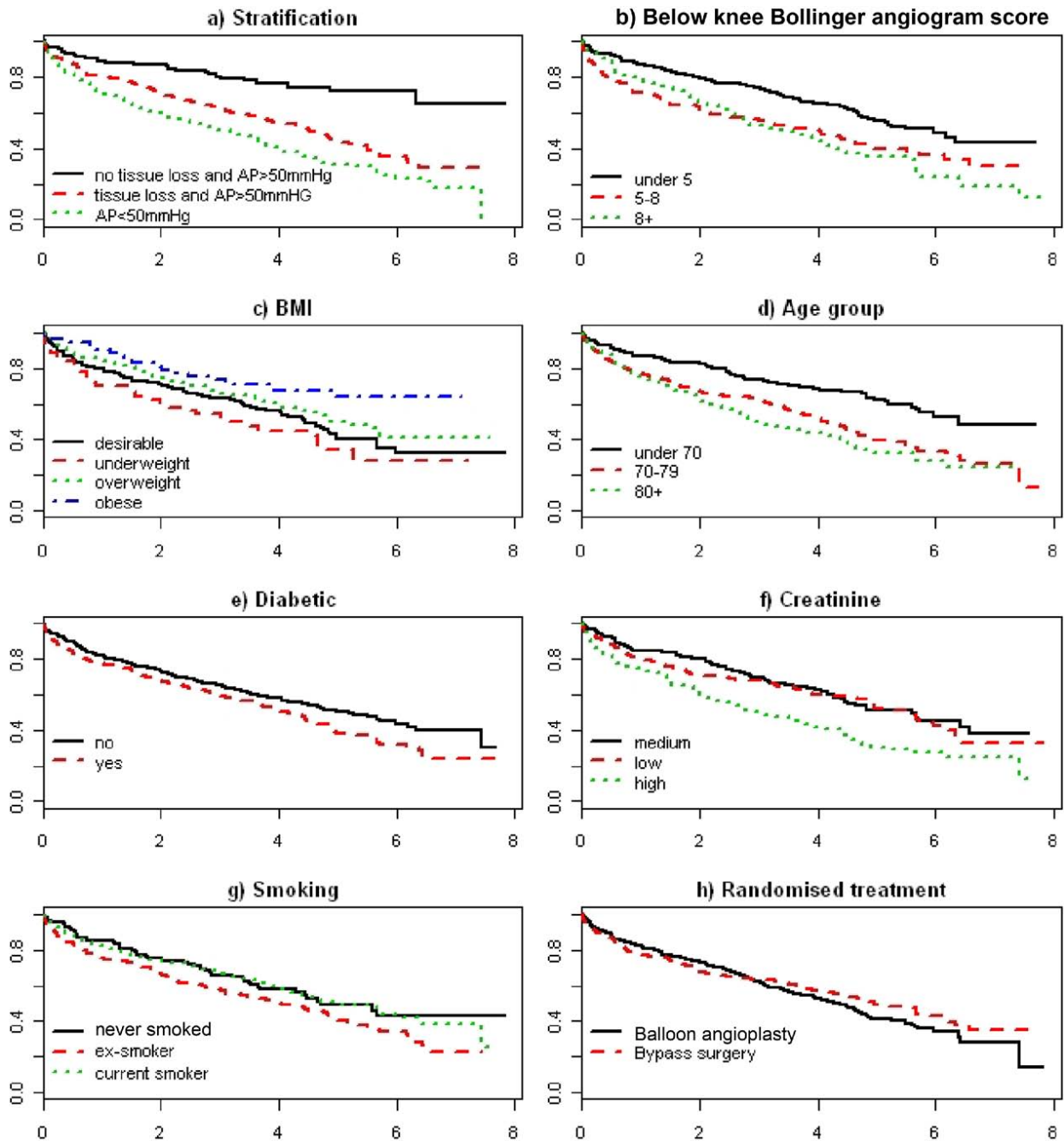


Fig 2. Survival by baseline covariates of (A) stratification, (B) below knee Bollinger angiogram score, (C) body mass index, (D) age group, (E), diabetes (F) creatinine level, (G) smoking, and (H) randomized treatment. The x axis is time from randomization in years.

- Serum creatinine (log $\mu\text{mol/L}$)
- Smoking status (current, former, never)

Overall survival by each of these factors is shown in Figs 2, A to G, and Fig 2, H shows the survival by randomized treatment on the same scale for a comparison.

In the univariate analysis, current smokers had survival similar to nonsmokers, and exsmokers had poorer survival.

In the multivariate analysis, however, the association was as expected, with current smokers and exsmokers both having worse survival than nonsmokers.

The time dependence of each of the covariates over the follow-up time was checked in the multivariate model using a test for the correlation of the weighted residuals with time.⁶ The Bollinger above knee angiogram score was the only factor to

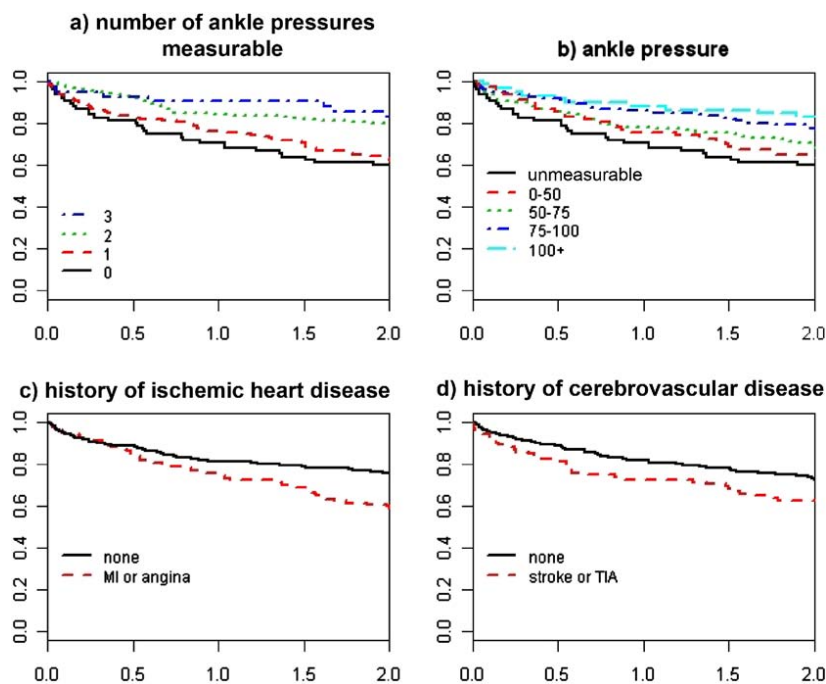


Fig 3. Overall survival to 2 years by additional predictors of (A) number of ankle pressures, (B) ankle pressure, (C) history of cerebrovascular disease, and (D) history of stroke. The x axis is time from randomization in years. *MI*, Myocardial infarction; *TIA*, transient ischemic attack.

show time dependence, but the effect was small and probably a false-positive result given the large number of effects examined.

The effect of randomized treatment on survival. The significant survival advantage, after 2 years, for patients randomized to BSX can be seen in Fig 2, H. The opposite is true in the earlier period, although this difference was not significant. For the whole follow-up period, the test for a time-dependent hazard was significant at $P = .028$.⁶

As reported elsewhere, this suggests that the clinical decision about whether a patient should receive BSX or BAP as first-line treatment for SLI should be informed, at least in part, by that patient's likelihood of surviving for >2 years.^{2,3}

Compared with the effect of the other baseline covariates, the effect of randomized treatment on survival up to 2 years is small. For that reason, the randomization group was excluded from the prognostic model.

Relationship between the survival to 2 years and baseline clinical factors (Weibull parametric regression). The data collected at baseline were examined to determine if there were any other factors that could improve the predictive model in addition to those already described.

Four further factors were selected; namely:

1. Number of ankle pressure measurements obtained (please see below)
2. The maximum ankle pressure obtained (when available)
3. History of MI or angina
4. History of stroke or TIA

The latter two were selected because they were the conditions that affected a substantial proportion of patients

and a priori were expected to affect survival. As was to be expected in this patient group, an examination of baseline ankle pressures in the trial leg showed many cases where one or more of the three possible ankle pressures (dorsalis pedis, posterior tibial, and perforating peroneal) were classed as "not detectable." We postulated that the number of detectable ankle signals might be a useful (novel) marker, in addition to actual ankle pressure (whose measurement can sometimes be difficult in these patients), of disease burden and thus outcome, including survival.

The original randomization stratification was based on using a dichotomy of maximum ankle pressure >50 mm Hg and <50 mm Hg, with those cases where no pressure could be measured at any of the three sites classed as <50 mm Hg. However, as was described, a careful examination of the data showed that additional information could be gleaned in terms number of measurements that were possible and the actual value of the pressure obtained. In other words, the number of ankle signals detected—not just the maximum pressure—was highly predictive of mortality.

These insights and data led us to replace the randomization stratification ankle pressure group (≥ 50 vs <50 mm Hg) with the number of detectable ankle pressures and the highest ankle pressure. To retain the information in the stratification groups (Table II), we introduced a separate code for presence of tissue loss vs rest or night pain only.

Fig 3, A illustrates the survival out to 2 years by the number of ankle measurements obtained. The highest ankle pressure was strongly related to the number of measures obtained (Table III). Survival by highest ankle pressure for

Table III. Number of ankle pressures measurable by highest ankle pressure obtained

| Variable | Highest ankle pressure (mm Hg) | | | | | All |
|---------------------------------|--------------------------------|--------|-------|------|----|-----|
| | 100+ | 75-100 | 50-75 | 0-50 | NA | |
| Ankle pressures measurable, No. | | | | | | |
| None | 0 | 0 | 0 | 0 | 75 | 75 |
| One | 12 | 33 | 56 | 52 | 0 | 153 |
| Two | 31 | 71 | 57 | 24 | 0 | 183 |
| All three | 16 | 17 | 7 | 1 | 0 | 41 |
| All | 59 | 121 | 120 | 77 | 75 | 452 |

those patients where at least one ankle pressure could be measured, and survival by the presence of a history of MI/angina or stroke/TIA, or both, are shown, respectively, in Figs 3 B, C, and D.

The variables that were candidates for inclusion in the predictive model were the four new measures described above, those listed in Table II excluding the BASIL randomization stratification groupings, which were replaced as described above, and the TASC and Bollinger above knee angiography scores, which were omitted in order to have only one angiographic score (the below knee Bollinger angiogram score which was the most predictive) in the model.⁵

Development of training and validation data sets.

A training data set was selected that consisted of a random selection of 75% of the original data (339 cases), leaving the other 113 cases to form a validation data set. When the data set is not very large, the choice of which proportions to use in training and validation data sets can be difficult. A training set with too few cases may yield a poor prediction, and a validation data set with too few cases may make the interpretation of the validation results difficult. We decided that the former was more important and thus selected a larger training data set. Starting with all the variables mentioned above, we attempted to find a simpler model that might fit the data better. To do this, we used backward elimination with the option to remove any variables for which the grouped *P* value (for categories) was $>.1$. However, each case was considered in terms of the plausibility of the coefficients for the individual groups and retained if these seemed clinically reasonable and important. Continuous variables replaced groupings where effects appeared linear.

By following this process, we arrived at a final Weibull model that differed from the full model in that:

- Age was fitted as a continuous variable (range, 39-99 years in the BASIL cohort).
- The highest ankle pressure (for those with at least one value) was also fitted as a continuous variable. Although this was not significant in the final model, we retained it because it contributed in the expected direction and is widely used in everyday practice. The value of ankle pressure was set to zero when no signal was detected. This choice does not affect the fitted values because the number of ankle measurements detected was also included in the model.

- The below knee Bollinger scores were simplified to a mean value of <5 or ≥ 5 .
- Diabetes was no longer predictive once all the other variables were included and was omitted from the model.

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

Validation of the Weibull model. When data are used to select a model, the predictions will tend to be too extreme. We can correct for this by shrinking the individual predictions towards the mean. A very reasonable approximation to an appropriate shrinkage can be obtained by calculating a shrinkage factor.⁷ This is calculated as $\{[1-(df-2)]/k\}$, where *df* is the residual degrees of freedom used in fitting the model and *k* is the overall value of the χ^2 statistic for the final model. The linear predictors are then shrunk toward the mean value for the linear predictor by this factor. For this example, a shrinkage factor of about 0.75 is obtained. We can then check how well this shrinkage factor will correct any over-fitting by examining the fit obtained for the validation model.

Linear predictors for the fitted model were obtained for the training and validation data sets, and in each case, three equally sized groups were formed to make high, medium, and low groups. Fig 4, A compares the modelled survival for the three groups based on the training data with the empirical survival curves. The closeness of the observed and predicted survival curves indicates that the fit is excellent. As we would expect, the fit is poorer for the smaller validation data set; in particular, it is too "optimistic" for the groups with good survival (Fig 4, B). The shrunken estimates (Fig 4, C) correct this. Although they appear to under-fit the poor prediction group, this could just be a chance effect due to the small size of the prediction data set. Thus we recommend the shrunken predictor, with a shrinkage factor of 0.75, to be used for individual predictions.

Using the Weibull model to predict outcomes for future individual patients. The information in Table IV can be used to calculate an individual linear predictor for any combination of covariates. Although the model was developed and validated from the training data set, it would seem sensible to make predictions for future patients from all the data available. This linear predictor can then be shrunk toward the mean of the all the predictors, which has a value of 2.53 for prediction from the full data. The 2.53 figure is the mean value of the linear predictor for all the patients in the cohort. The

Table IV. Fitted linear predictor for the Weibull model (positive coefficients indicate better survival)

| | From training data (n = 339) | | | From full data (n = 452) | | |
|--|------------------------------|--------|--------|--------------------------|--------|--------|
| | Coefficient | SE | p | Coefficient | SE | p |
| Intercept | 7.5173 | 1.9591 | 0.000 | 8.0978 | 1.6526 | 0.000 |
| Tissue loss present | -1.0076 | 0.4965 | 0.042 | -0.8022 | 0.3765 | 0.033 |
| Serum creatinine (μmol/l) | | | | | | |
| Low (under 88) | -0.7211 | 0.4442 | 0.105 | -0.8176 | 0.3672 | 0.026 |
| High (over 115) | -0.5540 | 0.4448 | 0.213 | -0.7579 | 0.3582 | 0.034 |
| Missing | -0.9508 | 0.8279 | 0.251 | -0.9773 | 0.7357 | 0.184 |
| (BASE = Medium [88-115]) | | | | | | |
| Age (per year) | -0.0402 | 0.0223 | 0.071 | -0.0493 | 0.0184 | 0.007 |
| Below knee Bollinger score | | | | | | |
| 5 or over | -0.5761 | 0.4173 | 0.167 | -0.4798 | 0.3231 | 0.138 |
| Missing | -0.3269 | 0.7343 | 0.656 | -0.0529 | 0.6113 | 0.931 |
| (BASE = under 5) | | | | | | |
| Smoking | | | | | | |
| Ex smoker | -0.9940 | 0.4623 | 0.032 | -1.0895 | 0.3766 | 0.004 |
| Smoker | -0.7838 | 0.5259 | 0.136 | -0.8427 | 0.4220 | 0.046 |
| (BASE = Never smoked) | | | | | | |
| BMI | | | | | | |
| Underweight (<20) | -0.7086 | 0.5109 | 0.165 | -0.5839 | 0.3997 | 0.144 |
| Overweight (>25) | 0.0063 | 0.4431 | 0.989 | 0.0247 | 0.3644 | 0.946 |
| Obese (>30) | 1.4336 | 0.7347 | 0.051 | 0.7739 | 0.5280 | 0.143 |
| Missing | -0.1274 | 0.4611 | 0.782 | -0.2181 | 0.3479 | 0.531 |
| (BASE = desirable [20-25]) | | | | | | |
| Number of ankle pressure measurements possible | | | | | | |
| One | -0.3731 | 0.6237 | 0.02 | -0.2598 | 0.4829 | 0.008 |
| Two | 0.5030 | 0.6987 | F-test | 0.4233 | 0.5634 | F test |
| All three | 0.6558 | 1.0380 | | 0.7943 | 0.8245 | |
| (BASE = None) | | | | | | |
| History of MI or angina | -0.8781 | 0.3706 | 0.018 | -0.7451 | 0.2814 | 0.008 |
| History of stroke or TIA | -0.5810 | 0.3755 | 0.122 | -0.5666 | 0.2996 | 0.059 |
| Highest ankle pressure (mm Hg)* | 0.0086 | 0.0075 | 0.247 | 0.0066 | 0.0060 | 0.269 |
| log(1/Shape factor) | 0.450 | 0.095 | <0.001 | 0.364 | 0.082 | <0.001 |
| Shape factor | 0.6376 | | | 0.6949 | | |

MI, Myocardial infarction; TIA, transient ischemic attack.

*Note that highest ankle pressure is set to zero if no ankle pressure readings could be obtained.

linear predictor is calculated for each patient from the regression coefficients in Table III and the patient's baseline characteristics. The formula for the shrunken predictor then becomes $[(2.53 + 0.75) \times (\text{linear predictor} - 2.53)]$. The probability of surviving to any time up to 2 years from the decision point can then be readily calculated from the Weibull survival function with a shape parameter of 0.696. Fig 5 is a histogram of this predicted probability for all 452 patients in the BASIL trial cohort.

To facilitate access to this tool should clinicians be interested in exploring it, we developed an Excel spread sheet (Microsoft, Richmond, Wash) that will be available for use by logging on to the BASIL trial Web site (<http://basiltrial.com>). A screen shot from this resource is illustrated in Fig 6. Table V illustrates the shrunken predicted survival probabilities for several hypothetical cases.

DISCUSSION

Reasons for undertaking the predictive analyses.

The aim of the BASIL trial was to determine whether, in patients requiring revascularization because of SLI due to infrainguinal arterial disease, a BSX-first or a BAP-first revascularization strategy was associated with a better out-

come in terms of AFS, OS, HRQOL, and use of hospital resources. An intention-to-treat analysis of randomized data censored in 2008 when >50% of patients had been monitored for >5 years confirmed that in patients who survive for 2 years after intervention, initial randomization to BSX was associated with a significant improvement of about 7 months in subsequent OS and a nonsignificant improvement of about 6 months in subsequent AFS. Having been presented with these data, the BASIL trial participants, as well as surgeons and interventionalists from many other countries, urged the trial investigators to construct a survival model that could help them judge which of their SLI patients might be likely to survive for ≥ 2 years and this enjoy the apparent longer term benefits of BSX.

The current article describes the development of a tool designed to estimate the chances of a BASIL-like SLI patient being alive 2 years after randomization. Although predicting HRQOL, functional status, patency, the quality of revascularization, and the risks of other major events such as amputation are important,⁸⁻¹⁰ we here confined ourselves to OS during the first 2 years. We did so because, according to the BASIL outcome data, being alive at 2 years appears to be the key factor that determines whether pa-

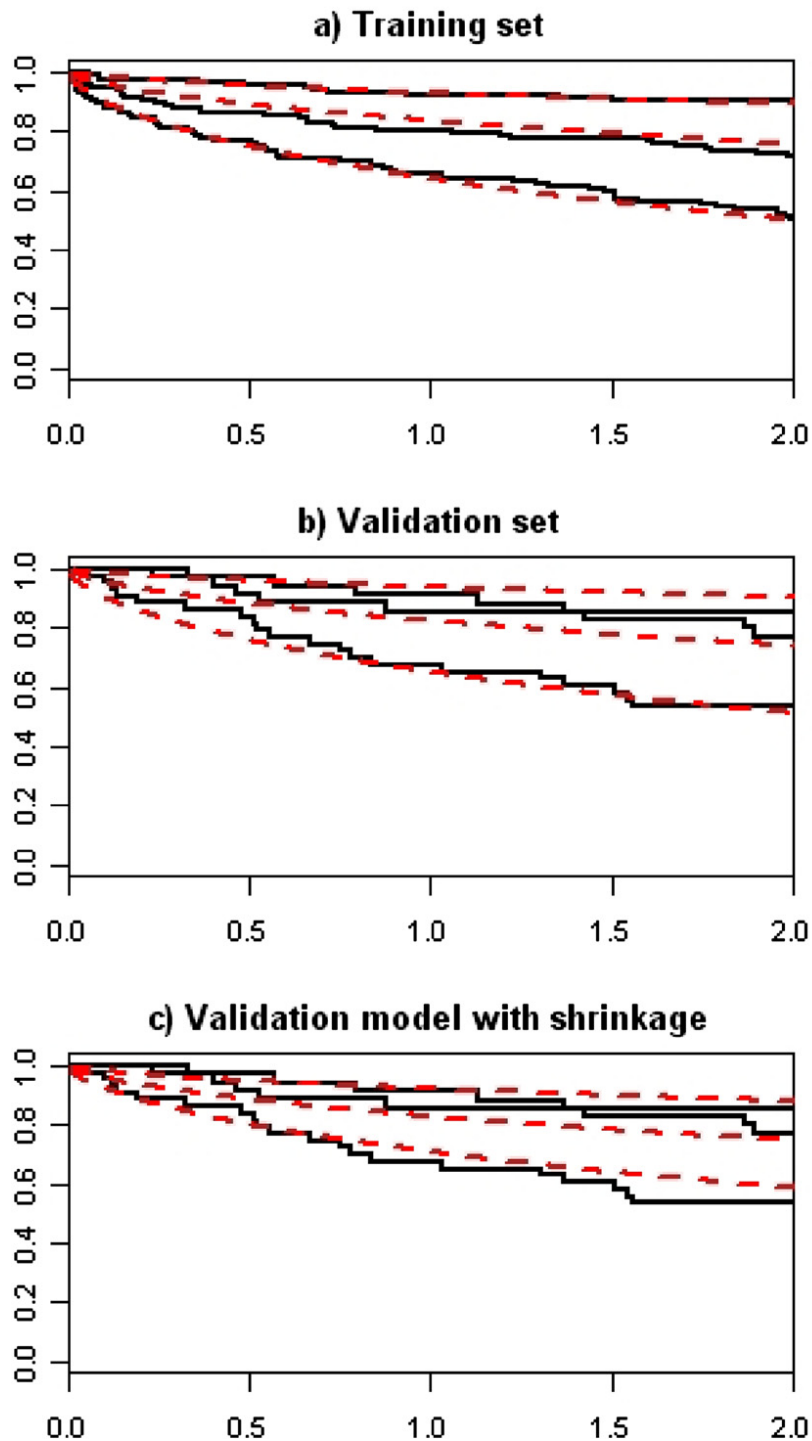


Fig 4. Fits to the (A) training and (B) validation data sets, and (C) validation model with shrinkage. In each case, three equally sized groups were created from the data according to the value of the linear predictor. The *dotted lines* show the fitted Weibull survival for the average linear predictor in each group. The *solid lines* are the Kaplan-Meier survival curves for each group.

tients are best served by a BSX-first or BAP-first revascularization strategy. We are well aware of the methodologic and interpretational challenges inherent in this work and that

the estimates of survival produced must be used with caution and in the context of the overall situation clinical situation for the individual patient.

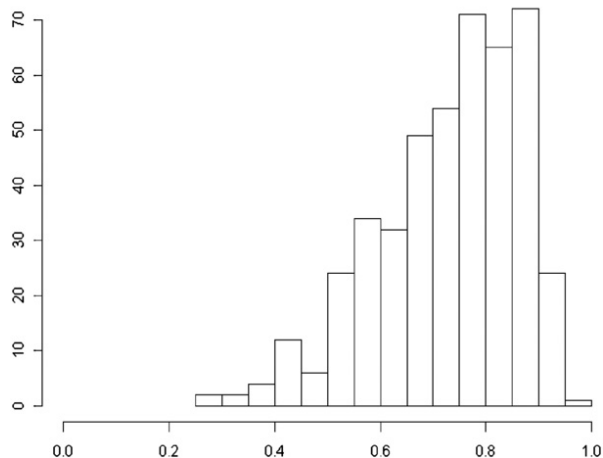


Fig 5. Probability of surviving to 2 years from randomization (shrunk estimate) for the 452 patients entered into the BASIL trial.

The results of the BASIL trial in general and the present analysis in particular confirm that, almost regardless of what revascularization treatment is offered, outcomes for AFS and OS are poor in patients with SLI. Thus, at the end of follow-up, slightly more than one-third of the patients were alive without major limb amputation of the trial leg, and less than one-half were still alive. Although most amputations and deaths occurred in the first year after randomization, the high event rate continued at between 10% and 20% per survivor-year thereafter. It is salutary to remember the form of revascularization a SLI patient receives from his or her surgeon or interventionalist appears to have a rather modest overall effect on outcome. The conclusion to be drawn from this is that the real key to improving the health of the nation as far as SLI is concerned lies primarily with better public health, early diagnosis, and aggressive best medical therapy, and probably not in the operating room or the interventional suite.

Previous attempts to predict outcomes in SLI. Many different groups of researchers have attempted to create models and scoring systems that will accurately predict individual patient outcomes after vascular interventions.^{11,12} It is argued that used across different health economies, such tools may:

- allow important clinical decisions to be made in a more scientific manner,
- improve the process of obtaining informed consent from patients,
- mitigate against medicolegal activity,
- allow a fair comparison of the performance of different clinicians and hospitals in the context of differing case-mix, and
- improve cost-effectiveness and value for money thus protecting patients, private health care providers, and the tax payer.

Efforts to create such tools are fraught with methodologic difficulties, however, and many surgeons and inter-

ventionalists choose not to use them. Instead, they prefer to rely on experience and intuition when making important clinical decisions about whether—and how—to treat their patients, including those with SLI. Although we do not want to devalue experience or the “art” of medicine, the problem with such an approach is that same patient may be offered a wide variety of different treatments depending on the clinician and institution he or she attends.^{13,14} This non-evidence-based variability in practice appears increasingly out of step with a respectable body of medical opinion. In the UK, for example, routine submission of detailed “score-able” prognostic patient data to the National Vascular Database for the purposes of comparative weighted outcomes analyses is increasingly viewed as a *sine qua non* of reasonable, defensible practice.¹²

As discussed above, although the present data confirm that all SLI patients are high risk, these patients actually represent an extremely heterogeneous group in their risks of death, limb loss, and other major cardiovascular events over different time horizons.^{2,3} As others have observed, this complicates clinical decision making,¹⁵ especially when trying balance short-term risks with longer-term durability in individuals who could reasonably be treated by either BSX or BAP.¹⁶ The same sort of trade-offs may pertain to other vascular conditions such as aortic aneurysm (open vs endovascular aneurysm repair) and carotid artery disease (surgery vs stenting).

Many previous groups have used observational, non-randomized data to predict various outcomes after interventions for SLI, and a small selection of the largest and most recent studies are briefly summarized here. Investigators who studied >4000 patients undergoing vein and prosthetic lower limb bypass in >100 Veterans Affairs (VA) hospitals in the United States were able to stratify the risks of major amputation and death during a median follow-up of 44 months. They concluded that risk indices derived from the preoperative workup may be useful to clinicians in assessing and communicating risks and prognosis, and that risk-adjustment of outcomes is critical for evaluating future therapies in such patients.¹⁷ Low cardiac ejection fraction predicted a significantly shortened 2-year survival after infrainguinal arterial reconstruction and a trend toward increased perioperative major adverse clinical events.¹⁸

In a large series of diabetic patients undergoing saphenous vein grafts for lower limb ischemia, investigators reported that they could predict 100% mortality at a median of 4 years follow-up by using just four factors.¹⁹

Within the Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT) III cohort of 1404 patients undergoing infrainguinal vein bypass surgery for CLI, a parsimonious risk stratification model (PIII risk score) reliably identified a category of CLI patients with a >50% chance of death or major amputation at 1 year.¹⁵

Going forward, the hope is that the application of these, and perhaps the BASIL risk scoring system, may result in patients with a poor prognosis being spared the risk, morbidity, and cost of such BSX, and perhaps being offered BAP or conservative treatment instead.

| Use menus or enter values in blue cells to describe the case of interest | | | | |
|--|---|--------------------------|--------------------|----------------------|
| Notes | Patient characteristics | | Results | |
| | Tissue loss | Yes | Time from decision | Proportion surviving |
| | BMI | 20-25 | | |
| | Creatinine | low | 6 months | 71% |
| | Lower Bollinger Score | 5 or over | 1 year | 57% |
| Enter 40 if below 40 and 95 if over 95 | Age | 79 | 2 years | 40% |
| | Smoking | Ex smoker | | |
| | Any history of MI/angina | hist of mi | | |
| | Any history of stroke/TIA | no history of stroke/TIA | | |
| Ankle pressure measurements attempted at Dorsal pedis or Posterior tibial and perforating peroneal | Number of ankle pressures measured* | 0 | | |
| Enter 0 if no ankle pressures obtained | Ankle Pressure (highest obtained in mmHg) | 0 | | |

Fig 6. Screen shot from prediction spreadsheet. MI, Myocardial infarction; TIA, transient ischemic attack.

Table V. Predicted 6 month, 1 and 2 year survival for 5 patients based on baseline data entered into the Weibull parametric survival model

| Characteristics of 5 BASIL patients with varying predicted 1 and 2 year survivals | | | | | |
|---|-----------------|------------|---------------------------------|----------------|----------------|
| | A | B | C | D | E |
| Smoking status | Ex-smoker | Ex-smoker | Current smoker | Current smoker | Current smoker |
| BMI | Desirable range | Overweight | Desirable range | Underweight | Overweight |
| Serum creatinine | Low | Low | Low | Low | Low |
| Tissue loss? | Yes | Yes | Yes | Yes | No |
| Number of ankle pressures detected | None | One | One | Two | All 3 |
| Highest ankle pressure | 0 | 60 | 30 | 56 | 136 |
| Below knee Bollinger score | 5 or more | missing | under 5 | under 5 | under 5 |
| History MI/angina? | Yes | No | Yes | No | No |
| History stroke/TIA? | No | No | No | No | No |
| Age (years) | 79 | 80 | 63 | 56 | 59 |
| | | | <i>Predicted % surviving to</i> | | |
| 6 months | 71 | 84 | 90 | 97 | 97 |
| 1 year | 57 | 75 | 84 | 96 | 95 |
| 2years | 40 | 63 | 76 | 93 | 92 |

Choice of variables to go into the models. How did we choose the baseline variables to examine? Why we did not use other variables such as functional status, socioeconomic status, cultural factors, medical therapy, and race and ethnicity, which some may consider equally, perhaps more, important? There is an almost limitless set of data that one could try to collect on every SLI patient due to undergo revascularization in an attempt to predict with perfect accuracy the likely outcomes for each possible treatment methodology. This is logistically and ethically impossible. Furthermore, from a scientific viewpoint, such a “fishing exercise” is likely to demonstrate very nicely the law of diminishing returns as the data collected will become increasingly confounded and its collection per se will perturb, perhaps adversely, the true baseline state of the patient; thus, some selection and discretion must be exercised.¹⁹

Clinicians have told us that they want a survival model based on robust (objective) baseline variables that are easily and widely available in day-to-day clinical practice at the

point of clinical decision making with respect to pursuing a BSX-first or BAP-first strategy for their patients. When the BASIL trial was designed in 1997 and 1998, we discussed at length (as all trialists do) what information should be collected at baseline and during follow-up. Collect too little and readers may consider that the trial patients have been inadequately reported, leading to a lack of confidence in the trial outcomes. Collect too much, however, and the data quality and completeness will inevitably deteriorate and prompt accusations of “fishing.”

The problem with considering racial, social, economic, and cultural factors in any prediction model is that they are difficult to define for the purposes of scientific reporting and do not travel well across national borders. For example, certain baseline variables, such as race,¹⁰ socioeconomic class, and educational attainment,^{20,21} that may be considered important in parts of the world with different health economies than the UK, are relatively less important per se

in the UK (and arguably in other European countries) where the population affected by peripheral arterial disease (SLI) is largely white and where all citizens are granted equal access to high-quality free health care and education at the point of delivery funded through general taxation.

The reviewers have asked us to specifically discuss the question of race and how that might affect the epidemiology of SLI, outcomes from lower limb interventions, and the appropriateness of generalizing the BASIL trial results and predictive modelling to other parts of the world. Although with a growing and ageing nonwhite population this may well change in the future, the UK population presenting to the National Health Service with SLI for revascularization is currently largely (>90%) white, a statistic reflected in the BASIL trial cohort.^{22,23} The question is whether this limits the usefulness of the BASIL trial and the current modelling in much of the rest of the world where this may not be the case.

Studies aimed at examining the links between race and ethnicity and the epidemiology and health outcomes from PAD, including SLI, are bedevilled with methodologic problems; perhaps not surprisingly, therefore, the resulting data are inconsistent and conflicting.^{20,22,23} Some reports have found no effect for race after adjusting for social class and educational attainment,²¹ whereas others have found ethnicity is a strong and independent risk factor for PAD that is not explained by higher levels of diabetes, hypertension, and body mass index.²⁴

Some have suggested that African American status has a negative affect on the long-term outcome of infrapopliteal revascularization, regardless of disease stage or associated risk factors.²⁵ Further, it has been hypothesized that such patients are biologically different in a way, as yet unknown, that may adversely affect the results of lower limb vein bypass.¹⁰

Whether for socioeconomic or biologic reasons, or both, data from the United States do appear to show a striking continuing difference in health care outcomes for white and African American citizens affected by PAD.²⁶⁻²⁸ A critical analysis of the literature shows that the data on racial, social, economic, and cultural factors in these patients are limited methodologically and that the conclusions, even apparently from within a single country such as the United States, are conflicting and largely unexplained to everyone's satisfaction.

Much of the predictive power of socioeconomic factors on cardiovascular diseases operates through other factors like smoking and pre-existing disease, which are already in our model. However, great care must be taken when considering outcomes reported in observational case series and controlled trials, such as BASIL, whose cohorts may not reflect the nature of the unmet need in any particular country, especially where universal health care coverage is not offered.

The reviewers have asked us to specifically discuss the low level of medical therapy observed in the BASIL trial, the effect of that on outcomes (especially survival), and why we did not include statin use, for example, in our predictive

model. It is certainly the case that we previously reported disappointingly low levels of best medical therapy being implemented in patients at the time of randomization into the BASIL trial.² One would like to think that this simply reflects the study recruitment period and represents a historical problem, now largely resolved. Regrettably, however, similar levels of under-treatment in PAD patients have been reported in recent large, prospective studies conducted in centers of excellence within wealthy countries with very well funded health care systems.²⁹⁻³¹

The question is whether one should include different levels of best medical therapy into the prediction model. It seems clear that statin use, for example, is associated with decreased cardiovascular mortality^{30,32} and amputation risk³³ in SLI patients. However, we took the view that because there is overwhelming level 1 evidence that every SLI patient should be considered for antiplatelet agents and lipid-lowering therapy—and the great majority should be taking these agents—regardless of baseline cholesterol,³⁴ we should not include these in our model. We are aware that others may take a different view, and that in the future, newer classes of drugs may also be shown to improve overall outcomes from lower limb revascularization.³⁵

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

Factors predictive of survival in the current model

The factors that were the most important predictors of BASIL trial patient survival were as follows:

Age, history of MI or stroke, and tissue loss. It is widely reported that older patients, especially those aged >80 years, are more likely to suffer complications and poorer outcomes after endovascular³⁶ and surgical interventions for lower limb ischemia. The fact that significant previous cardiovascular and cerebrovascular disease and the presence of ischemic tissue loss rather than only ischemic rest pain portends a poor survival is not unexpected.³⁷

Ankle pressure and number of detectable ankle pressures. We have been asked by the reviewers to comment specifically on a number of aspects of this part of our analysis.

What about abnormally high ankle pressures? Although we are aware of epidemiologic data showing that an abnormally high ankle pressure and pressure index (>1.4) may

predict an adverse cardiovascular outcome, we did not find this in an exploratory analysis that divided the ankle pressure data into groups. This observation may not, therefore, be transferable from population (often screening) studies (where it presumably reflects vessel incompressibility and may be a surrogate marker for diabetes, which was of course included in our model) to patients with SLI, very few of whom are likely to exhibit such high pressures. It is important not to extrapolate the analysis and interpretation of the current data beyond the boundaries of the trial; they only apply to patients randomized in BASIL and patients like them. We have data on preintervention and postintervention ankle pressures and pressure indices. These are currently being analyzed and will be reported in a further separate article in due course.

Why was ankle pressure not significant in the final model? The reason why ankle pressure was not *significant* in the final model is because it is correlated with the number of ankle measurements obtained. However, as we have explained, ankle pressure did add a little to the final model and in the direction expected, although not meeting the formal requirement for a significant effect. Statistical research suggests that a minimum value of $P = .05$ may be too strict for deciding on which predictors to include in a prognostic model. We also believe that a model that did not include ankle pressure might be difficult for clinicians to appreciate and that it was preferable to include it.

Could the authors perform a subgroup analysis of patients with true CLI (ie, those who meet either the European or Society of Vascular Surgery Rutherford classification of CLI)? We could, but we did not think it was helpful or necessary. Our modelling already takes into account ankle pressures and can be equally well applied to those with and without "true" CLI based on a cutoff of 50 mm Hg. This cutoff is somewhat arbitrary: Why not 45 or 55 or 60 mm Hg? We believe that the ankle pressure metric is better used as a continuous variable.

We also know that measuring ankle pressures accurately in these patients is difficult and associated with high levels of interobserver and intraobserver error that may take a patient's value alternately above and below the 50 mm Hg threshold.³⁸ Does that mean they have limb-threatening CLI today but not tomorrow? Obviously not, and this may be why we found the number of ankle pressures was a better predictor than the highest ankle pressure. It is important to point out that the unique property of the BASIL trial, which sets it apart from all other studies in the field, is that the data are randomized. This means that there were same proportion of patients with tissue loss, and the same proportion patients with ankle pressures < 50 mm Hg, in each group.

Serum creatinine. It is widely recognized and reported that even moderate impairment of renal function, as quantified, for example, by serum creatinine³⁹ or estimated glomerular filtration rate,⁴⁰ independently predicts mortality in vascular patients whether or not they undergo dialysis.^{28,41-43}

Smoking. It is no surprise that continued smoking predicts a poor outcome in these patients. Smoking histories are notoriously unreliable, however, and we did not supplement self-reported smoking status with objective testing.^{37,44}

Body mass index. We have found excess mortality in underweight individuals. This observation, termed the "obesity paradox," has been reported before in vascular patients and is thought to be possibly explained by an over-representation of individuals with moderate-to-severe chronic obstructive pulmonary disease (COPD) or other chronic disease.⁴⁵ Others have found that despite a higher rate of perioperative technical difficulties and morbidity (especially wound infections), obese patients undergoing lower extremity arterial revascularizations have similar long-term patency, limb salvage, and survival rates as nonobese patients.⁴⁶

Below knee Bollinger angiogram score. Research shows increasing severity of lower limb disease, as measured by ankle pressures and the ankle-brachial pressure index, is associated with increasing mortality, regardless of whether the patients have symptomatic lower limb disease. The anatomic and hemodynamic burden of disease also affects outcomes after surgical and endovascular lower limb interventions.^{5,47}

Diabetes. It is widely, although not universally, reported that diabetic patients fare less well in terms of AFS and OS after surgical and endovascular interventions for lower limb ischemia.^{19,28,45-47} This may be at least partly because diabetic patients present with more advanced and distal (tibial) disease that reduces run-off.⁴⁸ Although the presence of diabetes was significant in the univariate Cox model, it was not significant in the multivariate model and was not included in the final Weibull model. At first this seems counterintuitive. However, we have to ask why diabetes is a marker for poor outcomes in patients undergoing peripheral vascular interventions. Is it the diabetes per se, or as suggested above, is it the type of lower limb arterial disease that tends to develop in diabetic patients? We also have to recognize that a significant proportion of nondiabetic patients also present with a difficult-to-treat distal and typically heavily calcified disease. It is perhaps not surprising then that if one enters factors into a model that accurately reflect this disease severity (number of ankle pressures detectable, highest ankle pressure, Bollinger below knee angiographic scoring), they will (as we have shown here) be more powerful predictors of survival than diabetic status per se.^{49,50}

Issues of selection, generalizability, and applicability. One of the criticisms most frequently levelled at RCTs is their perceived lack of generalizability because of how the patients are selected for entry. The BASIL trial is no exception. Because, as requested by clinicians, we have tried to develop a predictive model that might be useful outside of the confines of the BASIL trial, the reviewers have quite rightly strongly challenged us on this issue and requested that we deal with it robustly. We are very pleased to be given the opportunity to do so.

As discussed at some length elsewhere, the BASIL trial investigators do not accept the premise that the BASIL trial patients have been “highly selected” in the pejorative sense of the term and that this selectivity undermines the validity of the trial findings.³ It is clear that every RCT has to select patients in the sense that only those patients for whom the treatment options on offer are appropriate can be invited to participate. Thus, BASIL is emphatically not a trial of all patients with SLI any more than other RCTs have been a study of all aneurysms, or all carotid artery disease, or all claudicant patients, for example. Rather, BASIL is a trial of those SLI patients whose disease is due to infrainguinal disease, who require immediate or early revascularization, and in whom the responsible surgeons and interventionalists determined there was a “gray area of equipoise” on the best manner in which to achieve that revascularization. This is the “uncertainty principle” that underpins all RCTs and makes them possible. Not to “select” in this way would be unethical and highly inappropriate scientifically.

This paradigm has been the bedrock upon which all other major vascular surgical and interventional trials have been built, and BASIL is no different. Thus, the landmark trials of interventions for carotid disease, aneurysms, and claudication did not randomize every patient with the condition but only those in whom there was reasonable doubt about what was best for the patient.

By conducting and publishing the BASIL audit data in 2005, we believe we provided considerably more information than most other reports on how the patients randomized were numerated from the denominator of all patients presenting with SLI due to infrainguinal disease.² Specifically, about one-third of all patients presenting to the 27 participating hospitals with SLI due to infrainguinal disease and who required immediate or early revascularization were considered to be in the “gray area of clinical equipoise” with respect to the relative merits of a BSX-first vs a BAP-first strategy for revascularization.

Given the often entrenched views on this issue that are found in the literature and quantified in the Delphi consensus studies undertaken as a prelude to the BASIL trial,^{12,13} this was in reality a surprisingly (pleasingly) high proportion. All of these patients were invited to enter the trial, and about 70% agreed. Given the nature of the patients and their condition, we think this is an impressively high proportion that compares very favorably with other landmark vascular trials. That so many patients were randomized and that most underwent the assigned treatment in a timely manner reflect great credit on the teams in each of the participating hospitals.

Lastly, in reporting the BASIL trial outcomes, we have attempted to describe in as much detail as possible the clinical and anatomic (angiographic) characteristics of the patients randomized.⁵ We hope that by doing so readers will be able to make informed judgments about what extent their patients are either similar to or dissimilar from those randomized in BASIL and decide to use or not use the trial data and modelling accordingly as part of their decision making practice.

How might the modelling be used in clinical practice? The results presented here have tried to meet a clear and present demand from fellow physicians for a clinically useful survival-prediction tool based on the BASIL data. We have presented a method of predicting survival for the type of patients in the BASIL trial using clinical and anatomic (angiographic) baseline factors, all of which are easily obtainable in routine clinical practice. Notwithstanding the important issues of generalizability and the considerable methodologic and interpretational difficulties inherent in these sorts of analyses discussed above, the specific intention here is to give clinicians an idea of how long an individual patient (similar to those randomized in BASIL) might live. The clinician can choose to use that information along with other data to counsel the patient, reach a decision about what treatment might be best, and take informed consent.

If the model suggests that the patient only has a 10% chance of being alive at 2 years, then BASIL suggests that a BSX-first strategy is not justified because of the associated increased morbidity and costs. Rather, the appropriate choice would seem to be BAP, or as one reviewer suggested, perhaps primary amputation or symptomatic best medical and nursing treatment only. However, if the model predicts a 90% chance that the patient will be alive at 2 years, then the BASIL trial data suggest that a BSX-first strategy is preferable because the patient will probably survive to enjoy the longer-term benefits of BSX in terms of AFS and OS at no significant additional cost.

If the model predicts a 50/50 chance of the patient being alive in 2 years, then that is helpful also. In this case the decision whether to attempt BSX or BAP can reasonably be decided on other factors, for example, relative availability of institutional expertise with the two techniques, cost, and importantly, patient choice, based on a full discussion of the likely medical journey the patient will take after each of the two strategies as described in the BASIL trial clinical outcomes reports. Used properly, as suggested above, we think our model is a useful tool in the clinician's armamentarium.

With regard to validation, BASIL is the only RCT to examine this issue and this is the only survival model based on level 1 data. We would be delighted if others were to make the brave commitment to undertake further RCTs in this field and help validate—or not, as the case may be—our findings.

In reality, we and probably many others tend to make these sorts of everyday but very important clinical judgments about our SLI patients on the basis of no level 1 evidence; we have to because there is not much such evidence. Although not wishing to entirely dismiss the “art” of medicine, the problem is that experience and intuition lead different clinicians to make very different decisions. We see that phenomenon every day in our hospitals and we quantified it in our Delphi consensus papers as a prelude to BASIL. Notwithstanding the considerable difficulties of so doing, with BASIL we are trying to take the decision regarding the choice of surgery or angioplasty when there is true uncertainty forward by applying at least

some scientific rigor. We know not everyone will like our methods or conclusions; we invite such colleagues to do the further randomized studies that are clearly needed.

Lastly, as alluded to by one of our reviewers, we can also use this type of prediction methodology to define the characteristics of a group of patients whose outcomes are so poor, regardless of what method is used to try to revascularize their leg, that they would probably be better served by amputation or medical (symptomatic) treatment only. The question of how to identify and manage these patients will be the subject of a further separate report.

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APPENDIX

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