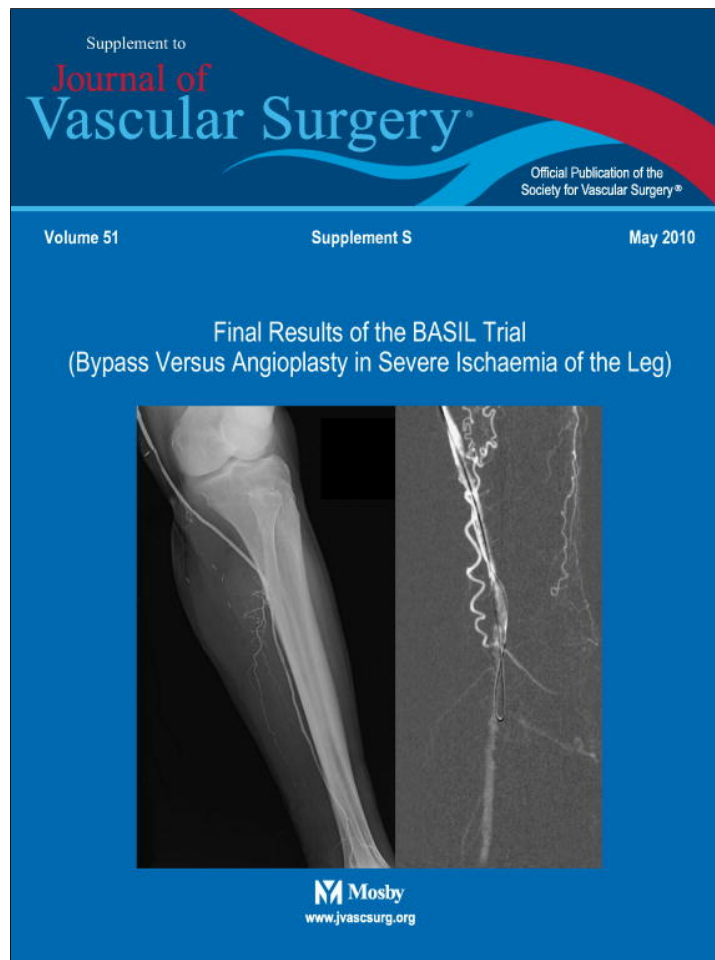


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Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial in perspective

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In the United Kingdom (UK) through the 1990s, there had developed an increasing trend in certain high-profile vascular centers toward treating patients with limb-threatening lower limb ischemia by means of (subintimal) balloon angioplasty (BAP) rather than traditional bypass surgery (BSX) in an attempt to reduce the morbidity, mortality, and costs associated with intervention. Although uncontrolled observational series suggested that BAP could be associated with acceptable limb salvage rates, at least in the short-term, previous studies comparing BSX and BAP had all had serious methodologic limitations.^{1,2} As a result, vascular surgeons and some interventional radiologists feared that the non-evidence-based trend toward BAP for severe limb ischemia (SLI), defined by rest/night pain, with or without tissue loss, might be associated with sub-optimal clinical outcomes and might not represent best use of limited National Health Service (NHS) resources. Many believed that the time for a randomized controlled trial (RCT) had come.³

In 1996 the UK National Institute of Health Research (NIHR) Health Technology Assessment (HTA) program (<http://www.hta.ac.uk/>) invited applications for funding to conduct a RCT to compare the clinical and cost-effectiveness of BAP vs BSX in SLI. Our group was fortunate enough to be awarded the commission.

At the time, the Principal Investigator (PI) was working in Edinburgh and the proposal was to undertake the study in eight vascular units within Scotland and one in the north of England. Through a series of meetings with participating vascular surgeons and interventional radiologists, the trial protocol was honed, finalized, and agreed to by the HTA. The trial came to be known as the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial.

It is fair to say that there was some skepticism within the UK vascular community that the BASIL trial would ever enroll enough patients. This was largely because many believed that surgeons and radiologists, so often entrenched in their view of which treatment was better, would refuse to randomize the patients under their care. There was also some concern that when offered the choice of major surgery or angioplasty, a much less invasive procedure, these elderly, infirm patients (or their families) would refuse randomization even if offered.

It is also worth remembering that although nowadays we take large pragmatic RCTs for granted—and indeed expect them to be available to guide practice—that was not the case 10 to 15 years ago. One senior surgeon apologized to the PI at the outset of the trial, saying that he could never put his patients in an RCT because it would mean he would have to confess that he was not sure how best to treat them. His view was by no means a solitary one at the time.

And so began a concerted effort to demonstrate to surgical and interventional colleagues in the various participating centers, and beyond, that there was, indeed, a wide “gray area of clinical equipoise.” This public relations campaign involved presentations at numerous local and national meetings and the undertaking of a Delphi consensus study among (potential) participants.⁴ As we expected, these Delphi studies revealed very substantial disagreements between and among vascular surgeons and interventional radiologists about the appropriateness of BSX or BAP for SLI due to infrainguinal disease.^{5,6} Participants were, of course, already aware of the wide variety of views on this issue. However, having seen for the first time the levels of disagreement quantified, and how their own views and practice compared with those of their peers, most participants significantly softened their objections to the randomization process.

Ethical approval was granted, the trial was registered, the data monitoring committee and trial steering group were convened, and the BASIL trial coordinator and research nurses were appointed. The first patient was randomized in August 1999. The PI was soon after appointed to the Chair of Vascular Surgery in Birmingham, and this resulted in the trial office and several key staff relocating from Edinburgh to the Heart of England NHS Trust in the West Midlands of England during early 2000. This put back recruitment, and the HTA kindly awarded a 12-month unfunded extension in recognition of the logistical problems following on from the relocation.

Although initially difficult, the move to England in 2000 did open up the possibility of greatly increasing the

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catchment population and the number of centers (eventually to 27). In retrospect, it seems likely that the trial would not have enrolled enough patients had it remained confined to the centers in Scotland.

The increase in centers and the results of the Delphi consensus studies greatly increased the rate of randomization, and by June 2004, 452 patients had been randomized and recruitment was stopped because the power calculation had specified 450 patients.

Overall, about 50% of patients presenting to these UK vascular centers with SLI underwent immediate or early revascularization; for a variety of reasons, the other 50% were treated conservatively in the first instance. Of those patients being considered for immediate or early revascularization, approximately 30% were found to be eligible for randomization because the responsible consultant surgeon *and* interventional radiologist believed it was appropriate to offer the patient either BSX or BAP in the first instance; in the other 70% of patients, the vascular team had a clear preference for either BSX or BAP. Of these eligible patients, about 70% entered the trial, a high proportion by RCT standards and a testament to the enthusiasm of the teams in the 27 recruiting hospitals.

Trial patients were well matched in terms of baseline clinical characteristics, angiographic severity, and extent of disease: >40% patients had diabetes, more than one-third were still smoking, three-quarters had tissue loss, about one-third had a highest ankle pressure <50 mm Hg, one-quarter had bilateral SLI, and most were elderly, with a significant cardiovascular medical history. Despite this, at the time of referral to vascular units, one-third of patients were not receiving an antiplatelet agent and only one-third was receiving a statin.

In the BSX arm of the trial, approximately 25% of the bypasses were of prosthetic material, and 90% of the vein bypasses were constructed using great saphenous vein. The distal anastomoses were fashioned in approximately equal numbers at the above knee popliteal, below knee popliteal, and crural arteries.

In about 70% of patients undergoing BAP, interventional radiologists attempted to treat a single length of disease (ie, an occlusion or critical stenosis); in the remainder, attempts were made to treat several (up to four) separate diseased lengths. The numbers of transluminal and subintimal BAP procedures were approximately equal, with just >10% being reported as mixed. Approximately 80% of the BAP patients underwent treatment of the superficial femoral artery either alone (about 40%) or combed with the popliteal artery (about 40%) and crural arteries (about 20%). Most of the remaining patients underwent treatment of the popliteal segments either alone, or more usually, combined with crural arteries; the number of isolated crural artery BAP was small.

INTERIM (2005) INTENTION-TO-TREAT ANALYSIS

An intention-to-treat analysis was undertaken during 2004 and 2005, and the trial outcomes were presented for

the first time at the UK Vascular Society meeting in November 2005. The results were published concurrently in *The Lancet*.⁷ At this stage, the trial showed that there was no difference in the main clinical outcomes of amputation-free survival (AFS) and overall survival (OS) between BSX and BAP out to 2 years but that BSX was about one-third more expensive in the short-term (first 12 months).

Originally, that was to be the end of the trial, but a post hoc analysis not specified in the statistical plan showed that after 2 years, those patients originally randomized to BSX were less likely subsequently to undergo amputation or to die. Although these differences were significant, the trial statistician advised caution, because the analysis was performed after the life tables had been viewed, and the numbers of end points were relatively small after 2 years. That said, the investigators and participants thought this finding was of such potential clinical significance that the trial should be extended; the HTA agreed and provided funding for a further period of follow-up.

In this *Journal of Vascular Surgery* supplement, the BASIL trial investigators and participants present the final analysis of the BASIL trial in terms of:

- clinical outcomes: AFS and OS by intention-to-treat and by treatment received (these analyses are presented separately because the authors believe it is very important not to conflate the analysis of randomized and nonrandomized data, please see below);
- health-related quality of life (HRQOL); and
- cost-effective use of hospital resources.

We also present:

- an analysis of preintervention angiograms so that readers can appreciate the extent and severity of the disease being treated in BASIL; and
- a Weibull survival model that examines baseline factors predicting survival of BASIL patients to 2 years, which appears to be the point in time where the relative merits of BSX and BAP change.

FINAL (2008) INTENTION-TO-TREAT ANALYSIS

For the final analysis, apart from four patients lost to follow-up, 100% of the patients had been monitored for 3 years and 54% for >5 years, and the longest follow-up was 7.7 years; 250 patients (56%) were dead, 168 (38%) were alive without amputation; and 30 (7%) were alive with amputation.

Considering the follow-up period as a whole, AFS and OS did not differ between randomized treatments. For those patients who survived 2 years, however, randomization to BSX was associated with a significant increase in OS of about 7 months and a trend toward increased AFS of about 6 months during the subsequent mean follow-up of about 3 years.

FINAL (2008) BY-TREATMENT-RECEIVED ANALYSIS

The investigators had not originally intended to undertake a by-treatment-received analysis of the trial because the

rigor of randomization is lost and a degree of bias is therefore inevitable. However, surgical and interventional colleagues urged us to reconsider, and we recognize that, provided it is interpreted with caution, such an analysis will provide some useful additional insights. However, the analysis is presented in a separate article to avoid conflation of randomized and nonrandomized data. This is a very important point, and so the senior editor asked that we add a little more explanation.

The intention-to-treat analysis compares patients randomized to a best endovascular (in most cases BAP alone) *first* or a best surgery (in most cases BSX) *first* revascularization strategy. This means that any differences in outcomes observed between the two groups are overwhelmingly likely to be due to true differences in the clinical and cost-effectiveness of the two strategies. This is why it is standard practice to analyze RCTs by intention-to-treat.

By contrast, if one chooses to study outcomes by which treatment was actually received, then the data inevitably reflect selection bias on the part of the surgeons and interventionalists or indeed the patients (and their families). Similarly, we did not randomize between vein and prosthetic BSX, or between transluminal and subintimal BAP. So by-treatment-received comparisons of outcomes offer a much lower level of evidence than do intention-to-treat analyses of randomized data; hence, the evidential weight given to RCTs over all other forms of study design.

However, bearing those caveats in mind, in the by-treatment-received analyses, we found that vein performed significantly better than prosthetic BSX in terms of AFS but not OS. The data also suggested that most patients would have been better served by an attempt at BAP rather than prosthetic BSX if no suitable vein was available as a conduit. No differences were found between transluminal and subintimal BAP. Patients who underwent BSX after failed BAP fared significantly worse than those who underwent BSX as their first treatment. The reasons for this are not clear at the present time and require further exploration.

ANGIOGRAM SCORING

Preintervention angiograms were assessed using the Bollinger system by a panel of vascular surgeons and interventional radiologists unaware of the treatment received or patient outcomes.⁸ This was primarily to facilitate appropriate generalization of the trial data to other groups of SLI patients with similar lumenographic burdens of disease. We chose the Bollinger method over other classifications available at the inception of the trial because it provides detailed information on the extent and severity of atherosclerotic disease by segment.⁹ In particular, the Bollinger system allows a very precise description of the infrapopliteal disease burden, which the investigators believed was likely to have an important influence on outcome in this patient group.

As was to be expected from the randomization process, the two arms of the trial were well matched in terms of disease severity and extent. In patients with the least overall disease, the disease tended to be concentrated above the knee; but as the overall burden of disease increased, the popliteal and crural arteries became increasingly involved.

The posterior tibial was the worst affected crural artery, whereas the peroneal artery appeared relatively spared.

Although the Bollinger scores were generally related to the TransAtlantic Inter-Society Consensus (TASC) II classification, cases of significant disagreement also occurred.¹⁰ This was mainly because TASC II, unlike the Bollinger assessment, does not permit the collection of detailed information for infrapopliteal disease, which BASIL has confirmed has a powerful bearing on outcomes after intervention in this group of patients (please see below).

PREDICTING PATIENT OUTCOMES

Because the relative merits of a BSX-first vs a BAP-first revascularization strategy appear to change at about 2 years after randomization, a Weibull survival model was developed to predict the probability of survival to 2 years using baseline patient and angiographic characteristics. A combination of age; presence of tissue loss; smoking; a history of angina, myocardial infarction, stroke, or transient ischemic attack; serum creatinine; below-knee Bollinger angiogram score; body mass index; number of recordable ankle pressures; and highest ankle pressure was highly predictive of survival to more than 2 years after intervention.

HRQOL AND HEALTH ECONOMIC ANALYSIS

HRQOL was nonsignificantly better in the BSX group before and after randomization. Amputation was associated with a significant reduction in HRQOL. During the first year, hospital costs in patients randomized to BSX were significantly higher (mean difference, \$8469). By the end of 3 years, the cost differences were no longer significant and this remained the case out to 7 years. Most of the costs related to ward stays rather than to procedures or the use of high dependency and intensive care beds. BASIL patients spent an average of 5 to 6 weeks of their first postrandomization year in the hospital and then 2 to 3 weeks per year thereafter. A 36-month quality-adjusted perspective generates a mean quality-adjusted lifetime of 442 days for BAP and 452 days for BSX (not significant) at an estimated additional average hospital cost of \$5521. The 3-year cost per QALY point estimate for BSX compared with BAP is therefore \$184,492, indicating that BSX is unlikely to be cost-effective at conventional UK willingness to pay thresholds.

IMPLICATIONS FOR PRACTICE

The greatest gains in SLI may lie in early diagnosis, best medical therapy, and prompt referral. SLI in most BASIL patients had developed slowly over months, often years. Despite this, and being at exceptionally high overall cardiovascular risk, many patients:

- had never received best medical therapy for their multisystem atherosclerotic disease,
- were referred (too) late to vascular services for (successful) revascularization, and
- were far from medically optimized at the time of referral.

It seems likely, therefore, that the burden imposed by SLI in the UK and probably in many other developed and

developing countries could be significantly diminished by measures aimed at:

- detecting lower limb arterial disease at an earlier stage (before it becomes life and limb threatening),
- ensuring that all such patients are offered evidenced-based best medical therapy, and
- encouraging prompt referral to vascular services for specialist care.

Multidisciplinary teamwork. BASIL strongly suggests that the best outcomes for SLI are achieved when vascular surgeons and interventional radiologists work closely together with other professionals as part of a multidisciplinary team in specialized, high-volumes centers (<http://www.vascularsociety.org.uk/>).

Treatment recommendations based on BASIL trial data. In SLI due to infrainguinal disease requiring immediate or early revascularization, patients expected to live:

- <2 years should usually be offered BAP first because they are unlikely to reap the longer-term benefits of BSX and because BAP is significantly less expensive and morbid in the short-term.
- >2 years should usually be offered BSX first; the strength of this recommendation appears to be greatest where vein is available as the conduit.

Role of prosthetic BSX in the management of SLI. Many patients who could not undergo a vein BSX would probably have been better served by a first attempt at BAP than by prosthetic BSX. Surgeons should make every effort to use vein and view prosthetic material as a last resort.

Role of BAP in the management of SLI. The combined immediate technical and early clinical failure rate of infrainguinal BAP for SLI is high at around 25%. Patients who underwent BSX after failed BAP fared significantly worse than those who underwent BSX as their first procedure. So, BAP does not appear to be the “free shot” that it is often claimed to be. Whether failed BAP selects out patients who are going to do badly whatever treatment they receive, or whether a failed BAP per se reduces the chance of successful surgical revascularization, these data should be borne in mind when considering treatment strategies.

The role of amputation and the care of vascular amputees. In retrospect, the interests of a significant proportion of BASIL patients would probably have been better served by primary amputation, followed by high-quality rehabilitation, rather than often repeated and ultimately unsuccessful attempts at revascularization. Amputees tended to spend long periods on acute surgical wards where they consumed expensive acute resources while not often receiving the rehabilitation they required. At least in the UK, there would seem to be a need to rethink the role of amputation for SLI and the planning of services for vascular amputees so that the available NHS resources can be used in a more clinically and cost-effective manner.

RESEARCH RECOMMENDATIONS

The investigators suggest that further research is required in order to:

1. repeat the Delphi studies to determine whether, as a result of BASIL and other studies, there has been any convergence of views on the relative merits of BSX and BAP in SLI;
2. confirm or refute the BASIL findings and recommendations in further RCTs;
3. validate the BASIL trial survival prediction model in a separate cohort of SLI patients;
4. examine the clinical results and cost-effectiveness of new endovascular techniques and devices in the management of SLI;
5. compare, within the confines of an RCT, (endovascular) revascularization vs primary amputation vs best medical/nursing care only in those SLI patients with the poorest overall survival prospects; and
6. model the longer-term cost-effectiveness of BSX and BAP and the possible gains and losses associated with an allocation mechanism that assigns initial treatment on the basis of expected survival.

We respectfully suggest that it is not in the public interest that responsibility for such research should be left entirely with the private sector, where the direction of travel is understandably driven by commercial interests. The case for further publicly funded trials in this important and challenging area of vascular and endovascular surgery would seem clear.

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