

Comparison of immediate and long-term outcomes in men and women undergoing revascularisation for chronic limb threatening ischaemia (CLTI) in the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL-1) trial

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1 **Comparison of immediate and long-term outcomes in men and women**
2 **undergoing revascularisation for chronic limb threatening ischaemia**
3 **(CLTI) in the Bypass versus Angioplasty in Severe Ischaemia of the Leg**
4 **(BASIL-1) trial**

5 Short title: Benson et al. Sex differences and outcomes in the BASIL-1 trial

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1 What does this study/review add to the existing literature and how will it influence future
2 clinical practice:

3 Existing data comparing men and women after revascularisation have all been extrapolated
4 from retrospective cohort studies or national registries. The anatomical and clinical disease
5 severity within the datasets, treatment decisions and length of follow up is heterogeneous and
6 therefore difficult to draw reliable conclusions from. This study is the first to compare
7 outcomes for men and women in a randomised setting. It suggests that for infrainguinal
8 disease, men are in fact worse off than women after limb salvage procedures in the long term.

9

10 Key Words: Critical limb ischaemia; Chronic limb threatening ischaemia; Peripheral vascular
11 disease; Infrainguinal bypass; Angioplasty; Sex.

1 **Abstract**

2 Background: The reports from cohort studies comparing outcomes after revascularisation for
3 chronic limb threatening ischaemia (CLTI) between men and women remains controversial.
4 Anatomical and clinical disease severity is often heterogeneous, and treatment choice
5 influenced by a variety of clinician and patient factors. Our aim was to compare outcomes in
6 men and women entered into the only randomised study comparing bypass and angioplasty
7 for infra-inguinal disease causing severe limb ischaemia.

8 Methods: Data were obtained from BASIL-1 trial case record forms. Baseline demographics
9 were compared, and Cox proportional hazard models were used to examine the relationship
10 between sex and amputation free survival (AFS), overall survival (OS), and freedom from
11 major adverse limb events (FF-MALE) using a per-protocol analysis. Data was analysed
12 using a per-protocol analysis.

13 Results: 452 patients were randomized into the BASIL-1 from 1999-2004. At randomisation,
14 women were older and less likely to be smokers, to have diabetes, or to be on recommended
15 best medical therapy. Men were more likely to present with gangrene. Ankle brachial
16 pressure index (ABPI), post-revascularisation length of hospital stay, and 30-day morbidity
17 and mortality were similar for men and women. At 3 years, female sex was associated with
18 significantly better AFS (HR 0.65, 95% CI 0.47-0.89, $p < 0.01$), OS (HR 0.66 95% CI 0.46-
19 0.95, $p = 0.02$) and FF-MALE (HR 0.74, 95% CI 0.57-0.96, $p = 0.02$).

20 Conclusion: In the BASIL-1 trial, women had similar short-term, but better long-term
21 outcomes after revascularisation. Sex is an important consideration when developing early,
22 evidence-based treatment pathway and revascularisation strategies for CLTI, and is an
23 independent risk factor for outcomes following revascularisation as well as development of
24 symptomatic PAD.

1 **Introduction**

2 Due to ageing populations, smoking, and diabetes, chronic limb threatening ischaemia
3 (CLTI) secondary to peripheral arterial disease (PAD) is an increasing global healthcare issue
4 (1). CLTI is the leading cause of limb loss, and an important cause of premature mortality,
5 worldwide (2). Although excess mortality has been reported in women suffering from other
6 vascular conditions, such as acute myocardial infarction (MI) and ruptured abdominal aortic
7 aneurysm (3–5), the influence of sex on outcomes following revascularisation specifically for
8 CLTI remains poorly defined. Thus, studies comparing men and women often fail to clearly
9 distinguish those with claudication or CLTI. The majority of CLTI studies exclude sex as a
10 significant co-variate, in part due to the relatively small number of women included, and the
11 results of those that do are contradictory (6–11). It is generally accepted that women
12 presenting with CLTI tend to be significantly older and less likely to be smokers than their
13 male counterparts (12). A disadvantage of cohort studies is their inability to assess for any
14 possible impact of clinician bias and/or patient choice on decisions regarding open or
15 endovascular revascularisation. Endovascular procedures are linked to shorter lengths of
16 stay and fewer immediate complications, therefore often selected in patients with higher
17 burdens of co-morbidity. This bias has implications for outcome reporting in a non-
18 randomised setting.

19 The UK NIHR HTA-funded Bypass versus Angioplasty in Severe Ischaemia of the Leg
20 (BASIL) trial remains the only randomised controlled trial (RCT) to have compared bypass
21 surgery (BS) first and balloon angioplasty (BA) first revascularisation strategies for CLTI
22 (13). The BASIL trial dataset offers a unique opportunity to examine the impact of sex on
23 outcomes following surgical and endovascular infra-inguinal revascularisation for CLTI, in a
24 randomised cohort. The aim of this study was to investigate the effect of sex on immediate
25 and long-term major adverse limb events (MALE), amputation free survival (AFS) and

1 overall survival for men and women after treatment out to 3 years. Secondary aims were to
2 compare incidence of cumulative re-intervention at 1 and 3 years following the primary
3 intervention.

4 **Methods**

5 The BASIL-1 trial:

6 The BASIL-1 trial methods have been published previously in detail(14). Ethical approval
7 was obtained from the Multi-Centre Research Ethics Committee for Scotland. Briefly,
8 between August 1999 and June 2004, 452 patients presenting to 27 UK hospitals with CLTI
9 due to infra-inguinal disease were randomised to a BS or BA first revascularisation strategy.
10 Patients were followed up to death or study end date. All surviving patients had a minimum
11 of 3 years of follow-up.

12 Definitions of Variables:

13 An ex-smoker was defined as some-one who reported that they had not smoked for at least
14 one year. Post-revascularisation morbidity was defined as major (above ankle) amputation,
15 myocardial infarction, cerebrovascular event, haematoma, infection (wound, chest, urinary
16 tract) or false aneurysm within 30-days.

17 Endpoints:

18 All analyses were performed based on the treatment received. Amputation free survival
19 (AFS) was defined as freedom from (above ankle) amputation or death from any cause. Re-
20 intervention was defined as any surgical bypass, angioplasty or ‘other surgical’ (non-bypass)
21 intervention on the index limb following primary intervention (this did not include major
22 amputation). Overall survival (OS) was defined as freedom from death from any cause.
23 Major adverse limb events (MALE) were defined as freedom from major amputation
24 (transtibial or above) or any major vascular reintervention such as thrombectomy or revision
25 of a failed graft in the index limb during the follow-up period. Time to event was taken as the

1 date of the first event. Cox proportional hazard models were used to examine the relationship
2 between sex and AFS, OS and MALE whilst adjusting for age, clinical presentation, ankle to
3 brachial pressure index (ABPI), and the type of revascularisation received. Time to event
4 analyses were presented using Kaplan-Meier plots. Analysis was performed using SAS
5 (version 9.4).

6

1 **Results**

2 The analysis included a total of 433 patients who underwent BA or BS as their first procedure
3 after randomisation. This cohort comprised 257 men (128 BS, 129 BA) and 176 women (67
4 BS and 109 BA). Baseline characteristics of men and women are shown in **Table 1**. Women
5 were older at randomization (74.2 vs 71.8, $p \leq 0.01$) and less likely to be smokers (36% of
6 women denied ever having smoked vs only 9% of men, $p \leq 0.01$). They were also more likely
7 to have untreated hypercholesterolaemia (15% of women vs 9% of men) and less likely to be
8 on an anti-platelet agent (56% vs 61% of men), although the differences were non-significant.
9 Rates of insulin dependent diabetes were similar, although men were more likely to suffer
10 from non-insulin dependent diabetes. Baseline creatinine was significantly higher in men
11 ($123 \pm 97 \mu\text{mol/L}$ vs $102 \pm 45 \mu\text{mol/L}$, $p \leq 0.01$). Although baseline ABPI were similar in men
12 and women, men were more likely to have a diagnosis of gangrene ($p \leq 0.05$). Baseline
13 mobility was similar. However more men had an existing diagnosis of PAD at randomisation
14 (19% vs 13% of women), and 17% vs 12% of women had already undergone a procedure in
15 the trial leg.

16 At 30-days, there was no difference in post-procedural morbidity (33% versus 29%),
17 mortality (4% vs 3%) or length of hospital stay. Although women showed a trend towards
18 shorter hospital stays (median LOS 11 [IQR 4-21] vs 15 [IQR 7-26]) negative binomial
19 model estimates failed to demonstrate an association. As expected, patients who underwent
20 surgical bypass spent longer in hospital (IRR 1.71[1.36-2.13] $p < 0.01$), as well as those
21 presenting with tissue loss (2.08 [1.69-2.56], $p < 0.01$).

22 **Table 2** shows the number of cumulative re-interventions at 1 and 3 year follow-up for men
23 and women after their primary intervention. Overall, rates of re-intervention in men and
24 women were similar. At 1 year, 27% of men and 26% of women had required further re-

1 intervention, and at 3-years 32% had undergone re-intervention in both groups. Logistic
2 regression models failed to find any significant factors affecting need for re-intervention
3 including sex, primary intervention or severity of clinical presentation.

4 However after 3 years, women were found to have a significantly better AFS (HR 0.65, CI
5 0.47, 0.89, $p < 0.01$) (Figure 1), OS (HR 0.66 (0.4634, 0.9487), $p = 0.02$) (Figure 2) and
6 MALE (HR 0.74 (0.57, 0.96), $p = 0.02$) (Figure 3). Assessment for differences in treatment
7 effect for sex was not statistically significant ($p = 0.2$ at 3 year follow up).

8

1 **Discussion**

2 Our findings add to previously published studies focusing on short term outcomes, either
3 survival to discharge or 30-day morbidity and mortality. Those studies often include a more
4 heterogenous population e.g. a mix of mild and severe limb ischaemia or claudicants and
5 CLTI, with differing anatomical patterns, and do not use ABPI values to classify presence of
6 critical ischaemia. Therefore the advantages of the BASIL cohort remains its well described
7 inclusion criteria of patients with CLTI, requiring infra-inguinal treatment. Although ABPI
8 was not part of the study inclusion criteria, values were available for inclusion in the analysis.
9 Although women were significantly older than men, with differing risk factor profiles at
10 presentation, the incidence of 30-day post-revascularisation morbidity and mortality were
11 similar to men, with better AFS, OS and MALE at long term follow up,. This fits with non-
12 randomised studies which have also noticed similar patterns of poorer outcomes for men in
13 the longer term (out to five years) related to higher incidence of cardiovascular related death
14 for equivalent optimisation(15). Our findings suggest that the deviation in outcomes begins
15 at between 1 and 3 years. It also suggests that post-intervention outcomes are influenced
16 heavily by factors already present at the point of presentation. If we wish to improve on the
17 disparities seen between men and women, we need to target epidemiological differences in
18 the community at the earliest manifestations of symptoms.

19 Although haemodynamic severity of disease (ABPI) was similar men were more likely to
20 present with gangrene or to have undergone a previous vascular intervention in the trial leg
21 prior randomisation. This suggests men were more likely to be undergoing redo procedures.
22 Redo surgery and the presence of tissue loss have previously been associated with worse
23 peri-operative outcomes compared to primary procedures and patients with rest pain
24 only(16,17). There are also likely to be major healthcare pathway differences between the
25 BASIL population and cohorts described in other published non-UK national registries.

1 There is likely to be more than one factor influencing the impact of sex on outcomes after
2 revascularisation. The randomised nature of the group allows us to remove one aspect of bias
3 relating to surgical approach. We have shown several baseline characteristics that differ
4 between the two groups, several of which are known to influence outcomes after
5 revascularisation. This suggests that by the time patients undergo intervention for SLI, sex-
6 based differences have already manifested themselves in the pre-operative care pathway.
7 There is awareness that women with PAD are underdiagnosed or diagnosed later, with
8 associated reductions in screening and management of associated risk factors(18).

9 Of note, 15/87 women (17%) randomised to receive bypass crossed over into the angioplasty
10 group, compared to 7/141 men (5%). As patients were technically suitable for both strategies
11 it could be hypothesised that baseline features led to a change in management. However this
12 cannot be proven with the available data.

13 Although further research, including an analysis of data from on-going UK NIHR HTA
14 funded RCTs such as BASIL 2(19) and 3(20), and BEST-CLI(21) will be required in order to
15 more fully define the relationship between sex and outcome for CLTI, present data from the
16 BASIL trial supports suggestions that sex is an important factor when considering evidence-
17 based revascularisation strategies. Poorer pre-operative pathways for women, suggested here
18 by reduced implementation and/or compliance with best medical therapy, indicate that there
19 are further gains to be made in the optimisation of any patient in earlier stages of peripheral
20 vascular disease.

21 Study Limitations: The trial recruited patients with rest pain or tissue loss, however an ankle
22 pressure of <50mmHg was not a requirement. Therefore the population was more
23 heterogeneous than a strict 'critical limb ischaemia' cohort. However, compared to large
24 registry data, many of which do not include ABPI to classify CLI, we have been able to use
25 ABPI in the modelling. Analysis of differences in sex for long-term outcomes was not in the

1 original BASIL protocol. Therefore, our findings are exploratory analyses used to generate
2 future hypothesis relating to strategies to improve outcomes for all patients undergoing
3 revascularisation for limb ischaemia. Finally, post-operative differences in anatomical
4 appearances post treatment in the two groups was not analysed in the original trial. Therefore
5 anatomical treatment success could not be included in the analysis.

6

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8 no specific funding for this work.

9 Disclosures: The authors have nothing to disclose

10 Conflicts of Interest: None

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