

A comparison of clinical outcomes following femoro-popliteal bypass or plain balloon angioplasty with selective bare metal stenting in the Bypass versus Angioplasty in Severe Ischaemia of the Limb (BASIL) trial

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1 **A comparison of clinical outcomes following femoro-**
2 **popliteal bypass or plain balloon angioplasty with selective**
3 **bare metal stenting in the Bypass versus Angioplasty in**
4 **Severe Ischaemia of the Limb (BASIL) trial**

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17 WHAT THIS PAPER ADDS

18 This by treatment received analysis of data from the publicly-funded, BASIL-1
19 randomised controlled trial confirms the superiority of bypass over plain balloon
20 angioplasty, with or without bare metal stenting, in patients with chronic limb
21 threatening ischaemia (CLTI) who require femoro-popliteal intervention. Although the
22 interventions were carried between 1999 and 2003, there are no more recently
23 acquired randomised data that contradict the findings presented here. BASIL-1 trial
24 data therefore remain an important and relevant standard with which to compare
25 outcomes in current vascular and endovascular practice and the results of on-going,
26 publicly funded, pragmatic randomised controlled trials such as BASIL-2, BASIL-3
27 and BEST-CLI.

28

29 **ABSTRACT**

30 Objective: To compare outcomes in patients with chronic limb threatening ischaemia
31 (CLTI) due to femoro-popliteal (FP), with or without infra-popliteal (IP), disease who
32 underwent FP (vein or synthetic) open surgical bypass (OSB) or plain balloon
33 angioplasty (PBA), with or without bare metal stenting (BMS), in the Bypass versus
34 Angioplasty in Severe Ischaemia of the Limb (BASIL-1) trial.

35 Method: Data were extracted from BASIL-1 case record forms. Outcomes reported
36 include immediate technical success, freedom from major adverse limb events (FF-
37 MALE) and further re-intervention (FF-R), amputation free survival (AFS), overall
38 survival (OS), and limb salvage (LS).

39 Results: Patients underwent primary OSB (n = 128; 89 vein, 39 synthetic) or primary
40 PBA (n = 183; 6 had BMS). Mean follow-up was 46.2 and 43.6 months respectively.
41 Patients were well matched at baseline except that PBA +/- BMS patients were
42 significantly more likely to be current smokers. There was no difference in overall or
43 IP (run-off) Bollinger angiogram scores between groups. Immediate technical
44 success was significantly higher for OSB (98% vs. 81%, p<0.0001). OSB was
45 associated with a longer mean index hospital admission (p=0.001) but there was no
46 difference in hospital days at 12 months. FF-MALE (HR 1.51, p=0.04) and FF-R
47 (HR=1.68, p=0.02), but not AFS (HR 1.18, p=0.4), OS (HR 1.14, p=0.5) and LS (HR
48 1.09, p=0.8) were significantly better following OSB.

49 Conclusion: Although AFS, OS and LS were similar in the two groups, OSB was
50 associated with significantly fewer MALE and re-interventions. So, while PBA +/-
51 BMS may be a less resource intensive (expensive) and morbid option in the short
52 term, this appears unlikely to be the case in the longer term. Present data add further
53 weight to the argument that, where possible, patients presenting with CLTI due to FP
54 disease should be offered OSB as their primary revascularisation procedure.

55

56 **INTRODUCTION**

57 The Bypass versus Angioplasty for Severe Ischaemia of the Leg trial, now known as
58 the BASIL-1 trial, remains the only published randomised controlled trial (RCT) to
59 have compared an open surgical bypass (OSB) first, with a plain balloon angioplasty,
60 with or without bare metal stenting, (PBA +/- BMS) first revascularisation strategy for
61 chronic limb threatening ischaemia (CLTI) due to infra-inguinal disease^{1,2}. In BASIL-
62 1, approximately 75% of patients had predominantly femoro-popliteal (FP) disease
63 and intervention while in about 25% the disease and intervention were predominantly
64 infra-popliteal (IP). A recently published BASIL-1 IP sub-group analysis showed that,
65 when compared to PBA (no IP BMS were used), a vein bypass (VB) first strategy
66 resulted in better overall survival (OS), amputation-free survival (AFS), and quality of
67 revascularisation (time to wound healing and relief of ischaemic rest pain)³. Despite
68 BASIL-1, the only currently available 'level 1' evidence, showing better long-term
69 clinical outcomes following OSB, there has nevertheless been a non-evidence-based
70 trend towards offering primary endovascular intervention to patients with CLTI due to
71 FP disease. The aim of this BASIL-1 sub-group analysis, therefore, is to compare
72 outcomes in patients who underwent FP OSB (VB and synthetic, SynB) or PBA +/-
73 BMS as their primary revascularisation procedure.

74

75 **METHOD**

76 *BASIL-1 trial*

77 BASIL-1 methods and ethical approvals have been published previously⁴. In brief,
78 between August 1999 and June 2004, 452 patients with CLTI due to infra-inguinal
79 disease were randomised to an OSB first or a PBA +/- BMS first revascularisation
80 strategy. Patients were eligible for trial inclusion if the responsible clinicians felt that
81 they required early revascularisation and were in clinical equipoise OSB and PBA +/-
82 BMS. Patients were followed up by six dedicated research nurses at 1, 3, 6, and 12
83 months post randomisation and then annually until death or 1 July 2007. The primary
84 endpoint was amputation free survival (AFS) and secondary end-points included
85 overall survival (OS), limb salvage (LS) and requirement for re-intervention. BASIL-1
86 was a multi-centre, pragmatic, clinical effectiveness RCT that allowed participating
87 units to continue to use their preferred post-intervention surveillance programmes.
88 However, the majority of the re-interventions were due to persisting or recurrent
89 symptoms and signs of CLTI.

90 *Inclusion criteria for FP subgroup analysis*

91 In order to be included in the current sub-group analysis, BASIL-1 patients had to
92 fulfil two criteria. Firstly, they had to have atherosclerotic FP disease causing CLTI
93 and, secondly, they only underwent intervention to the FP segment (with no IP
94 intervention). Baseline and clinical outcome data were extracted from the original
95 prospectively gathered BASIL-1 case record forms.

96 *Outcomes*

97 In this BASIL-1 FP sub-group analysis, we report immediate technical success (as
98 defined by the operating surgeon or interventionalist), mean length of index hospital
99 admission, days spent in hospital out to 12 months from randomisation, freedom
100 from major adverse limb events (FF-MALE) and re-intervention (FF-R), AFS, OS,
101 and LS. Major amputation was classified as amputation of the trial limb above the
102 ankle. We have chosen not to include minor amputation as a re-intervention as we
103 regard this as being mainly determined by the condition of the foot at presentation
104 and not the type of primary revascularisation. Major adverse limb event (MALE)
105 comprised any revascularisation attempt or major amputation of the trial limb during

106 follow up. Post-procedural complications are reported as 30-day mortality, morbidity
107 (complications and re-interventions) and major adverse cardiovascular event
108 (MACE) which comprises death, myocardial infarction or cerebrovascular event.
109 Unplanned interventions for post-operative complications, revascularisation (OSB or
110 PBA +/- BMS), or major amputation were collated and reported under the term
111 surgical re-interventions if they occurred within 30-days. No patients were lost to
112 follow up for the primary endpoint or the other secondary endpoints reported here.
113 Patients who partially withdrew had their clinical outcome data collected via UK
114 centralised data-bases, now known as ONS (office of national statistics) and HES
115 (hospital episode statistics) data.

116 *Statistics*

117 Time to event analyses comparing all OSB (VB and SynB) with PBA +/- BMS are
118 presented over a 7-year period using Kaplan-Meier plots and Log-Rank test for
119 significance. Hazard ratios were used to detect statistically important differences in
120 outcomes using 95% confidence intervals. Differences between the groups were
121 compared using t-test, χ^2 -squared and Wilcoxon Rank Sum tests according to
122 distribution of data using SAS v9.4.

123

124 RESULTS

125 *Demographics*

126 There were 311 patients; 128 underwent primary OSB (89 VB, 39 SynB) and 183
127 had primary PBA +/- BMS (6 stents). The mean follow-up was 46.2 (range 0-91) and
128 43.6 (range 0-93) months respectively. Ipsilateral great saphenous vein (GSV) was
129 used for 83 (93%) VB; arm vein was used for 1 (1%) and composite vein (arm and
130 leg vein spliced) for 5 (6%). Most VB were reversed (63, 71%) with (23, 26%) being
131 in-situ and (3, 4%) non-reversed. The two groups were very similar in terms of
132 baseline characteristics although PBA +/- BMS patients were more likely to be
133 current smokers, and there was a trend to more chronic obstructive pulmonary
134 disease (COPD) in OSB patients (**Table 1**).

135 *Distribution of Disease*

136 There was no significant difference in the overall burden of disease between the two
137 groups in terms of Bollinger angiographic scores ($p = 0.2$) (**Table 2**). IP disease
138 severity was also statistically similar in the two groups (Bollinger Score = 44.4 vs
139 46.6, $p=0.4$) with the peroneal artery being the least diseased run-off vessel.

140 *Short-term outcomes*

141 Immediate technical success was highly significantly better for OSB (98% vs. 81%,
142 $p<0.0001$). Although patients undergoing OSB had a longer median (inter-quartile
143 range, IQR) index hospital admission (16 [10-27] vs. 8 [2-19] days, $p=0.0001$) by 12
144 months patients in both groups had spent an equivalent median (range) number of
145 days (17 [11-28] vs 17 [6-41], $p=0.7$) in hospital. Statin use was low in both groups
146 (OSB 30% vs. PBA +/- BMS 37%, $p=0.2$). Antiplatelet use was significantly higher in
147 OSB patients (66% vs. 55% $p=0.05$). Although all-cause 30-day mortality was not
148 statistically different between the two groups, OSB patients suffered more morbidity;
149 in particular, wound infection (**Table 3**). PBA +/- BMS patients required more surgical
150 interventions within the first 30-days (2% vs. 7%, $p=0.06$).

151 *Long term clinical outcomes OSB vs PBA+/-BMS*

152 There was no difference in AFS (62% vs. 55%, HR 1.18, 95% CI 0.82-1.69, $p=0.4$)
153 (**Figure 1**), OS (69% vs. 63%, HR 1.14, 95% CI 0.77-1.70, $p=0.5$) (**Figure 2**) or LS

154 (85% vs. 85%, HR 1.09, 95% CI 0.59-2.01, p=0.8) between OSB and PBA+/-BMS.
155 However, FF-MALE (67% vs. 56%, HR 1.51, 95% CI 1.01–2.25, p=0.04) (**Figure 3**)
156 and FF-R (72% vs. 63%, HR=1.68, 95% CI: 1.09–2.60, p=0.02) (**Figure 4**) were
157 significantly lower following OSB. Resolution of rest pain (85% vs 76%, HR=0.84,
158 95%CI 0.63–1.11 p=0.2) and wound healing at 3 years (90% vs 84%, HR=0.78,
159 95%CI 0.55-1.10 p= 0.2) (**Figure 5**) were similar in the two groups.

160 *Long term clinical outcomes VB vs SynB vs PBA+/-BS*

161 There was no significant difference in AFS (67% vs. 51% vs 55%, p = 0.2), OS (72%
162 vs. 64% vs. 63%, p=0.4) (**Figure 7**) and LS (90% vs. 72% vs 85%, p=0.3) between
163 VB, SynB and PBA+/- BMS, although the number of SynB was small. FF-MALE
164 (71% vs 58% vs 56%, p=0.02) was significantly better following VB.

165 *Re-interventions*

166 Overall, 24 (19%) OSB, and 63 (34%) PBA +/- BMS, patients underwent re-
167 intervention, with 38 and 85 re-interventions respectively (**Table 4**). There was no
168 difference in the number of inflow procedures performed in each group (7 vs. 8,
169 p=0.2). Patients in the PBA +/- BMS group underwent more secondary bypass
170 procedures (47, 55% vs. 3, 8% p=<0.001) and more repeat angioplasties (21 ,25%,
171 vs 5, 13%, p=0.1). OSB patients underwent more angioplasties for in-graft stenosis
172 (13, 35% vs. 1, 1%, p=<0.001).

173

174 **DISCUSSION**

175 The main finding of this BASIL-1 FP sub-group analysis is that although major
176 amputation rates and all-cause mortality are similar, primary OSB, especially VB,
177 results in significantly fewer MALE and re-interventions than primary PBA+/-BMS.
178 So, although an endovascular first revascularisation strategy may be a less resource
179 intensive (expensive) and morbid option in the short term, in longer term, this seems
180 unlikely to be the case. Present data add further weight to the argument that, where
181 possible, VB should be offered as the preferred primary revascularisation procedure
182 to most patients presenting with CLTI due to FP disease. This is especially so in
183 standard risk patients (anticipated life expectancy >2 years) who are more likely to
184 enjoy the long-term benefit of VB and less likely to suffer short-term peri-operative
185 morbidity^{1,5-8}. Present data support the previously published BASIL-1 IP sub-group
186 outcomes indicating that the durability and quality of revascularisation are better after
187 VB than after PBA². In this BASIL-1 FP cohort, unlike in the IP cohort, healing of
188 tissue loss and speed of resolution of rest pain were not significantly different
189 between the two groups. This may be because almost a quarter (23%) of the
190 patients who underwent primary FP PBA +/- BMS required subsequent OSB for
191 persistent or recurrent symptoms of CLTI. Indeed, CLTI patients presenting with the
192 most severe disease in terms of wound, ischaemia and infection⁹, seem to be those
193 most likely to enjoy better outcomes following primary VB than primary endovascular
194 intervention. This is especially so given that outcomes following secondary VB after
195 failed primary endovascular intervention are significantly worse than those observed
196 when VB is used as the primary revascularisation procedure^{10,11}. The low rates of
197 best medical therapy (antiplatelet and statin use coupled with smoking cessation)
198 often observed in CLTI studies are worthy of discussion. In the present study, only
199 two-thirds of patients undergoing OSB were on antiplatelet therapy at randomisation
200 (the rate was 10% lower in PBA +/- BMS group) and only about one-third of patients
201 in both groups were on a statin. While better medical therapy is likely to improve
202 CLTI outcomes overall, there is no evidence this would have altered the conclusions
203 of BASIL-1 in terms of the recommendation to offer VB first wherever possible. Thus,
204 in a recent large case series⁸, although best medical therapy rates had improved to
205 approximately 80%, the re-intervention rate was 62% for OSB and 52% for PBA at 3
206 years. These 3 year re-intervention data are worse than those observed in BASIL-1

207 at 7 years. This is an important observation as endovascular enthusiasts often point
208 to the fact that BASIL-1 is now a relatively old trial (patients randomised between
209 1999 and 2004) and argue that, if BASIL-1 were to be repeated using modern
210 endovascular techniques and technologies, the trial would show a clear advantage in
211 favour of an endovascular first strategy for most, even perhaps all, patients. While
212 that is possible, there is no evidence to suggest that such an outcome is likely.
213 Indeed, the evidence we have suggests that such an outcome would be unlikely. In
214 particular, with regard to drug coated balloons (DCB) and drug eluting stents (DES),
215 there are no data to show that they improve clinical outcomes in patients with CLTI
216 when compared to PBA +/-BMS¹²⁻²². While DES and DES may be associated with
217 better anatomic outcomes, the great majority of the patients entered into the plethora
218 of industry-funded trials had intermittent claudication, underwent treatment of short
219 segment disease, and had short follow up with little or no reporting of clinical
220 outcomes. Even the small minority of patents in these trials who had CLTI were very
221 largely entered on the basis of rest pain and did not have tissue loss. Other
222 techniques such as laser atherectomy²³ and covered stents²⁴ have not been widely
223 adopted due to a lack of evidence demonstrating clinical and cost-effectiveness. At
224 the time of writing, there are no published, publicly-funded trials comparing DCB /
225 DES to either PBA or OSB in patients with CLTI. As a result, and given their very
226 considerable additional cost, the UK National Institute for Health and Care
227 Excellence (NICE) have recommended against the use of DCB and DES and are
228 awaiting the outcome of on-going RCTs, specifically BASIL-2²⁵ and BASIL-3²⁶ in the
229 UK and BEST-CLI trial²⁷ in the US before reconsidering the matter. The European
230 Society of Vascular Surgery (ESVS) and European Society of Cardiology (ESC)
231 guidelines on the diagnosis and treatment of patients with peripheral arterial disease
232²⁸ specifically state no clinical benefit has been proven for DCB over PBA. Data
233 reported here support the ESC/ESVS guidelines stance that vein bypass surgery for
234 long lesions in patients with CLTI is the first choice method of revascularisation. In
235 conclusion, this BASIL-1 FP sub-group confirms the superiority of VB as the
236 preferred primary FP re-vascularisation procedure for most CLTI patients. However,
237 the results of further publicly funded, pragmatic RCTs, such as BASIL-2, BASIL-3
238 and BEST-CLI, are required to help answer the many remaining questions regarding
239 the clinical and cost-effectiveness of alternative revascularisation strategies in
240 different subgroups of CLTI patients.

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354

355

356

357 **TABLES**

358 **Table 1. Baseline characteristics in patients undergoing open surgical bypass**
 359 **and plain balloon angioplasty +/- bare metal stent**

		OSB (n = 128)	PBA +/- BMS (n = 183)	P Value
Conduit	Vein	89 (70%)	-	
	Synthetic	39 (30%)	-	
	PBA+/-BMS	-	183 (100%)	
Gender	Male	78 (61%)	94 (51%)	0.09
Limb	Right	57 (45%)	75 (41%)	0.5
Age	Mean (SD)	71.7 (8.0)	73.1 (8.6)	0.2
Follow up (months)	Mean (SD)	46.2 (27.2)	43.6 (24.7)	0.4
Indication	Rest pain	52 (41%)	69 (38%)	0.4
	Tissue Loss	14 (11%)	14 (8%)	
	Both	62 (48%)	100 (54%)	
Creatinine	Mean (SD)	111.7 (79.4)	107.7 (60.2)	0.6
Smoker	Never	17 (13%)	36 (20%)	0.04
	Ex-Smoker	65 (51%)	67 (36%)	
	Current	46 (36%)	80 (44%)	
Diabetes Mellitus		47 (37%)	74 (40%)	0.5
Congestive Heart Failure		5 (4%)	8 (4%)	0.8
Hypertension		77 (60%)	108 (59%)	0.8
Coronary Artery Disease		35 (27%)	50 (27%)	1.0
Chronic Obstructive Airway Disease		19 (15%)	15 (8%)	0.06

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361 OSB open surgical bypass; PBA, plain balloon angioplasty; BMS, bare metal stent

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363 **Table 2. A comparison of mean (SD) Bollinger scores between open surgical**
 364 **bypass and plain balloon angioplasty +/- bare metal stent groups**

Arterial Section	OSB (n = 128)	PBA+/-BMS (n = 183)	P Value
Profunda Femoris	1.6 (2.6)	2.1 (3.4)	0.2
Proximal Superficial Femoral	7.0 (5.9)	7.0 (5.5)	0.9
Distal Superficial Femoral	10.3 (4.9)	10.2 (5.0)	0.8
Proximal Popliteal	6.9 (5.8)	7.1 (5.7)	0.7
Distal Popliteal	1.5 (2.5)	2.7 (4.4)	0.007
Tibio-peroneal Trunk	2.5 (3.6)	2.8 (4.3)	0.6
Proximal Posterior Tibial	6.8 (5.9)	8.2 (6.6)	0.05
Distal Posterior Tibial	8.3 (6.6)	9.3 (6.5)	0.1
Proximal Peroneal	4.4 (4.8)	4.6 (5.2)	0.7
Distal Peroneal	5.8 (6.2)	4.5 (5.6)	0.1
Proximal Anterior Tibial	6.0 (6.1)	5.8 (5.7)	0.8
Distal Anterior Tibial	7.2 (6.8)	6.7 (6.6)	0.6
Plantar	6.7 (4.0)	6.5 (4.4)	0.8
Total	70.7 (24.5)	75.1 (27.3)	0.2
Total Infra-popliteal Score	44.4 (22.4)	46.6 (24.1)	0.4

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368 **Table 3. Morbidity and mortality (30 day) in patients undergoing open surgical**
 369 **bypass and plain balloon angioplasty +/- bare metal stent**

	SB (n = 128)	PBA+/-BMS (n = 183)	P Value
Mortality (30 days)	7 (5%)	6 (3%)	0.3
Morbidity and mortality (30 days)	58 (45%)	59 (32%)	0.02
Myocardial infarction	5 (4%)	5 (3%)	0.6
Transient ischaemic attack	0 (-)	2 (1%)	0.2
Cerebrovascular accident	1 (1%)	3 (2%)	0.5
Haematoma (not operated)	7 (5%)	8 (4%)	0.7
Haematoma (operated)	2 (2%)	1 (1%)	0.4
Wound Infection	37 (29%)	29 (16%)	0.006
Lower respiratory tract infection	4 (3%)	5 (3%)	0.8
Urinary tract infection	2 (2%)	3 (2%)	1.0
False Aneurysm (not operated)	1 (1%)	0 (-)	0.2
False Aneurysm (operated)	0 (-)	0 (-)	-
Major Amputation	3 (2%)	9 (5%)	0.3
Surgical Intervention (30 days)	3 (2%)	13 (7%)	0.06
Major adverse cardiovascular event	10 (8%)	10 (5%)	0.4

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371 OSB open surgical bypass; PBA, plain balloon angioplasty; BMS, bare metal stent

372 *Wound Infection includes foot infection as well as infection at the intervention site

373

374 **Table 4. Re-interventions following open surgical bypass and plain balloon**
 375 **angioplasty +/- bare metal stent**

	Re-intervention	OSB (n = 128)	PBA+/-BMS (n = 183)
Number of patients		24 (19%)	63 (34%)
Total re-interventions		38	85
Inflow	Ileo-femoral bypass	2 (5%)	1 (1%)
	Iliac PBA+/- BMS	2 (5%)	4 (5%)
	Axillo-femoral bypass	1 (3%)	0 (0%)
	Aorto-bifemoral bypass	0 (0%)	1 (1%)
	Common femoral endarterectomy	1 (3%)	2 (2%)
	Femoro-femoral crossover	1 (3%)	0 (0%)
FP Revascularisations	OSB	3 (8%)	47 (55%)
	PBA+/-BMS	5 (13%)	21 (25%)
	Graft PBA	13 (34%)	1 (1%)
	Thrombolysis	1 (3%)	1 (1%)
	Embolectomy	3 (8%)	2 (2%)
	Profundoplasty	0 (0%)	2 (2%)
	Graft patch angioplasty	1 (3%)	0 (0%)
Other	Graft explanted for infection	2 (5%)	1 (1%)
	Haemostasis	2 (5%)	0 (0%)
	Chemical Sympathectomy	1 (3%)	2 (2%)

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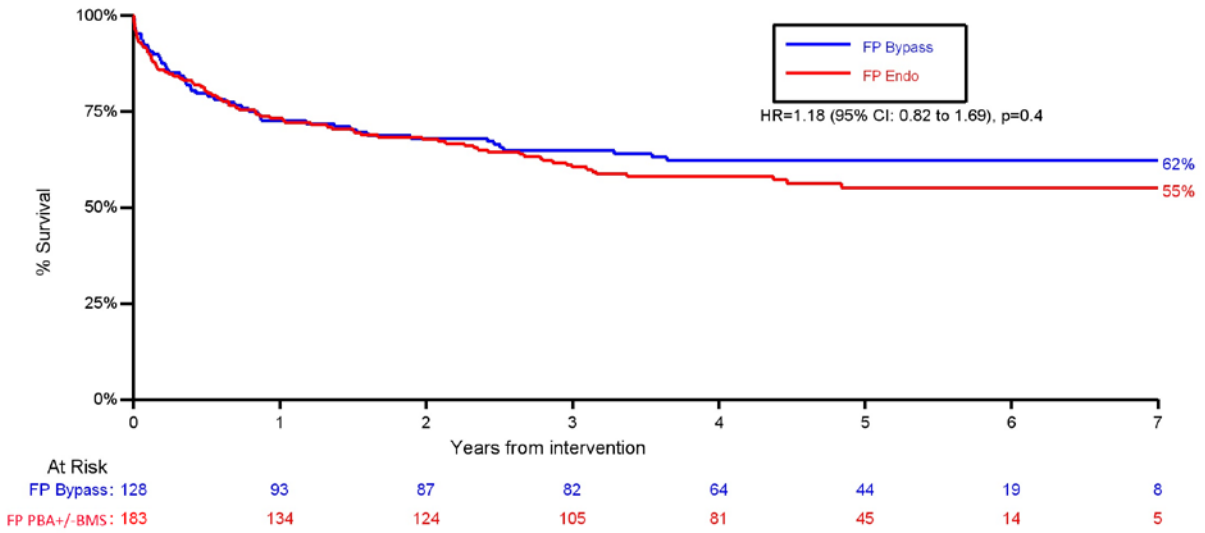
377 OSB open surgical bypass; PBA, plain balloon angioplasty; BMS, bare metal stent

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379 **FIGURES**

380 **Figure 1. Amputation free survival in patients undergoing femoro-popliteal**
 381 **bypass and plain balloon angioplasty +/- bare metal stent in the BASIL-1 trial**

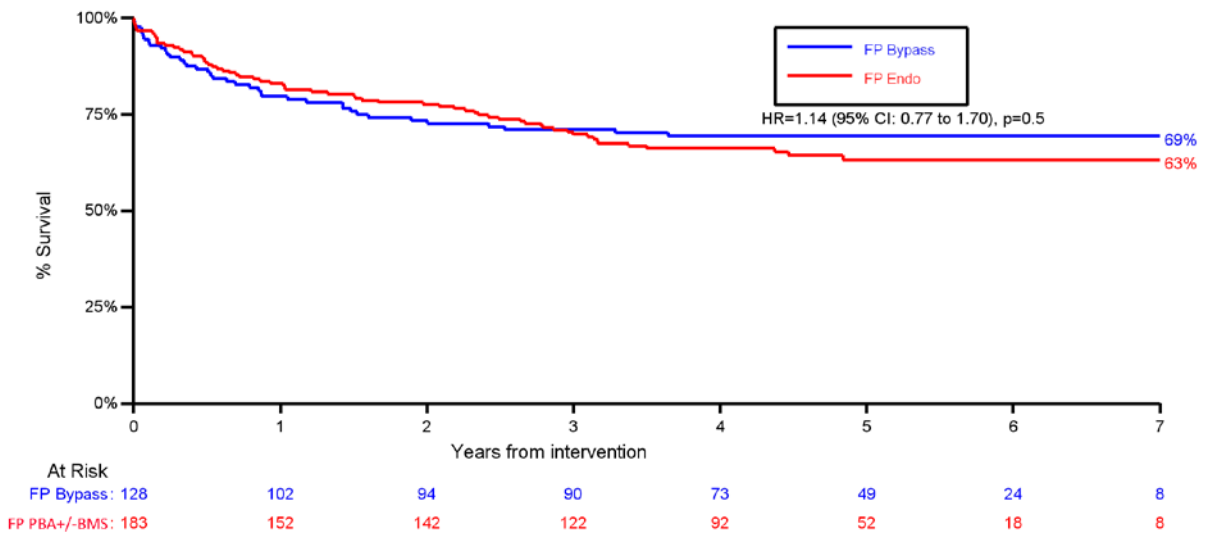
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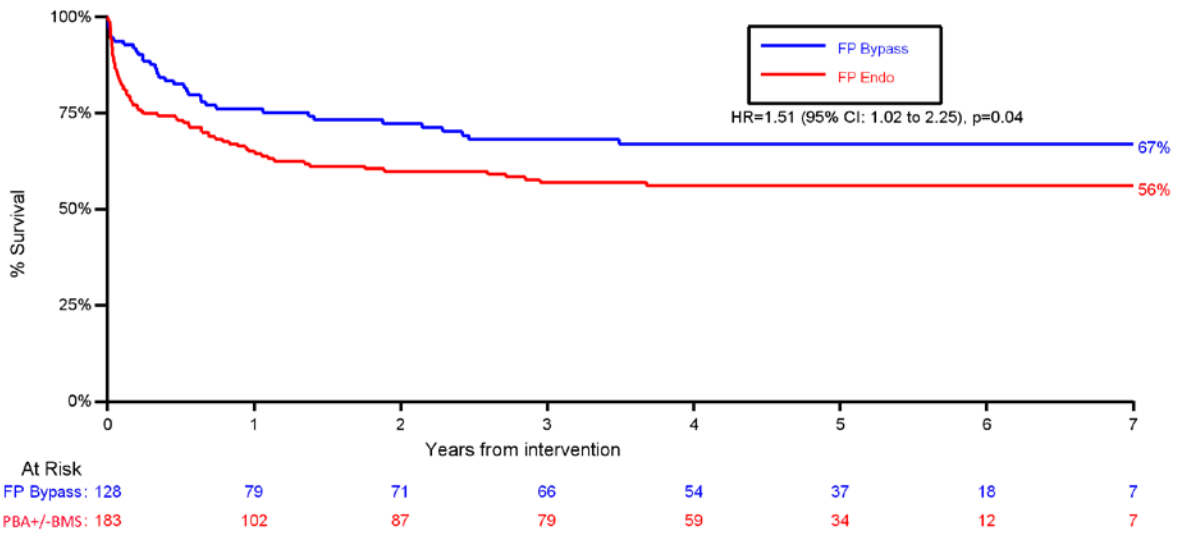
384 **Figure 2. Overall survival in patients undergoing femoro-popliteal bypass and**
 385 **plain balloon angioplasty +/- bare metal stent in the BASIL-1 trial**

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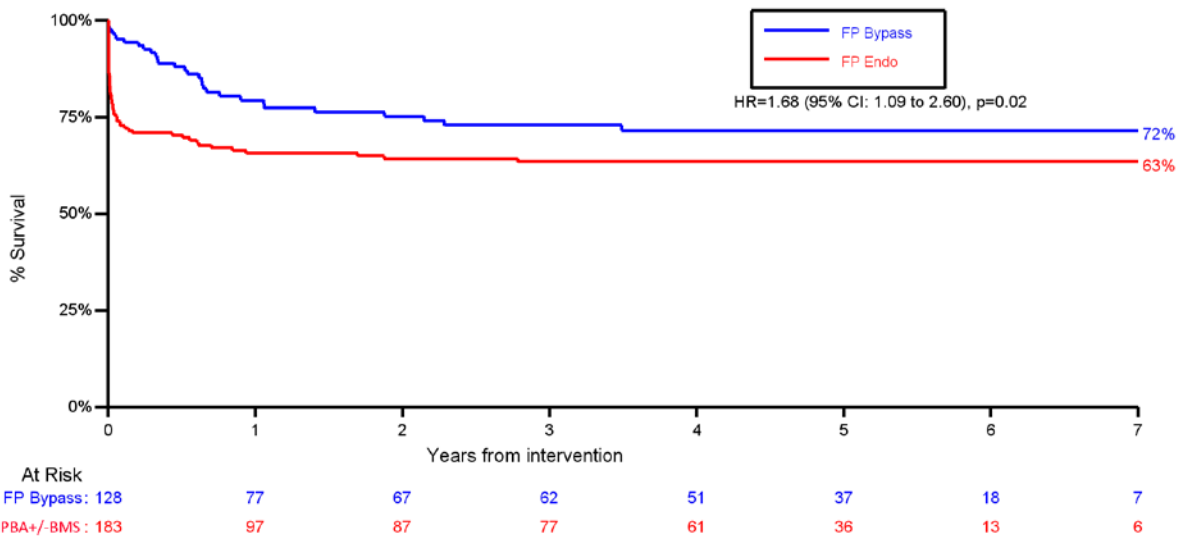
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388 **Figure 3. Freedom from major adverse limb events in patients undergoing**
 389 **femoro-popliteal bypass and plain balloon angioplasty +/- bare metal stent in**
 390 **the BASIL-1 trial**



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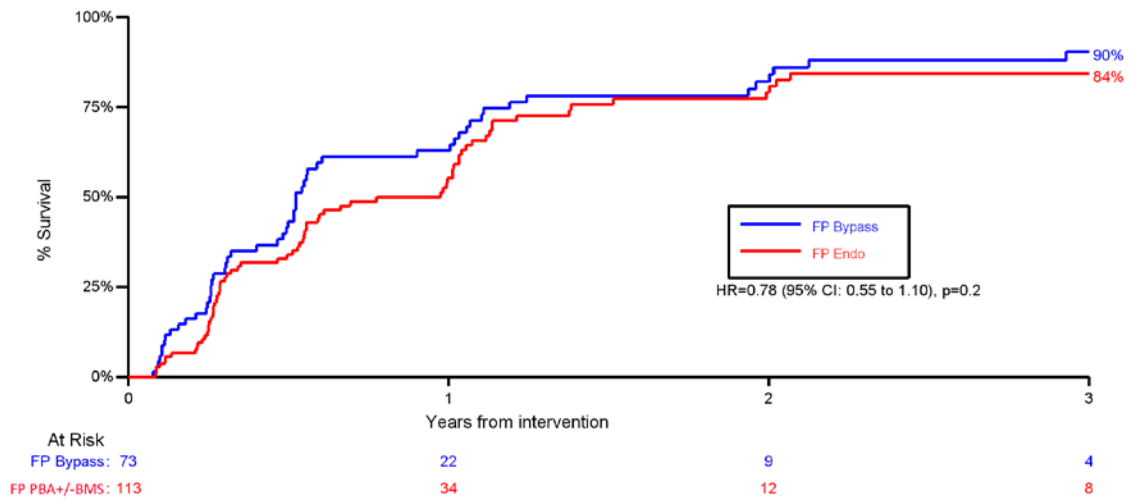
392 **Figure 4. Freedom from re-intervention in patients undergoing femoro-**
 393 **popliteal bypass and plain balloon angioplasty +/- bare metal stent in the**
 394 **BASIL-1 trial**



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396

397 **Figure 5. Wound Healing in patients undergoing femoro-popliteal bypass SB**
398 **and plain balloon angioplasty +/- bare metal stent in the BASIL-1 trial**



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