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Bypass After Failed Endovascular Intervention is Associated with an Increased Risk of Above Ankle Amputation Among Patients with Chronic Limb Threatening Ischaemia in a Randomised Trial Population*

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WHAT THIS PAPER ADDS

This secondary analysis of data from a prospective randomised clinical trial examined secondary bypass after an index endovascular intervention for chronic limb threatening ischaemia in patients deemed suitable for either open or endovascular interventions. Secondary bypass was associated with higher above ankle amputation rates than primary bypass, particularly in patients with an available single segment great saphenous vein.

Objective: One concern about the endovascular-first (ENDO) approach for chronic limb threatening ischaemia (CLTI) is whether bridges are burned for a secondary bypass (SB) if required in the future. This secondary analysis of a prospective randomised trial aimed to compare above ankle amputation rates in patients with CLTI treated with primary bypass (PB) compared with those treated with SB after an initial ENDO approach.

Methods: Data from the randomised unblinded Best Endovascular versus Best Surgical Therapy of Patients with CLTI (BEST-CLI) trial were analysed. Patients were included if they had CLTI and were considered as candidates for open or ENDO revascularisation with the primary outcomes being major adverse limb free event survival. There were two parallel cohorts based on whether single segment great saphenous vein (SSGSV) was (cohort 1) or was not (cohort 2) available. Primary bypass was compared with SB after index ENDO using the primary outcome of above ankle amputation with death as a competing risk. Multivariable and propensity matched analyses were performed.

Results: There were 665 PB and 158 SB in cohort 1 and 192 PB and 45 SB in cohort 2. Time to SB after ENDO occurred at a median of 28 days in all patients and median of 210 days in those who had a successful initial ENDO procedure. Unadjusted one year analysis showed SB to be associated with increased above ankle amputation (14% *vs*. 8.1%; $p = .002$) overall. Secondary bypass was associated with increased above ankle amputation in cohort 1 (13.5% *vs*. 7.4%; $p = .003$), whereas this was not statistically significant in cohort 2 (15.9% *vs*. 10.9%; $p = .28$). These findings were confirmed on multivariable analysis (adjusting for age, gender, wound ischaemia foot infection stage, randomisation strata, diabetes mellitus, end stage kidney disease, previous

index infrainguinal reconstruction, and smoking history) for cohort 1, with SB associated with increased above ankle amputation (HR 1.72, 95% CI 1.08 – 2.73; p = .02), remaining true when restricting to SB after a technically successful ENDO (HR 2.21, 95% CI 1.26 – 3.86; p =.005). Results were similar on propensity matched analyses.

Conclusion: In patients with CLTI deemed suitable for either open or ENDO, SB was associated with worse limb salvage compared with PB, particularly in patients with available SSGSV.

Keywords: Amputation, Bypass, Endovascular, Ischaemia

INTRODUCTION

Endovascular interventions (ENDO) are increasingly being performed as first line treatment for chronic limb threatening ischaemia (CLTI) and infrainguinal peripheral artery disease.[1,2] However, there is no clear evidence to support an aggressive endovascular first approach. It is also uncertain how such a strategy may affect long term limb specific outcomes, especially if a subsequent infrainguinal bypass is needed for inadequate or failed ENDO.[3–7]

An important consideration with an endovascular first approach for CLTI is whether bridges are burned with this strategy.[8–12] The concern centres around the idea that endovascular first interventions may compromise the value of a subsequent bypass, resulting in worse outcomes for the patient than if the first step in CLTI revascularisation is a bypass. Suggested reasons for this hypothesis include disruption of vulnerable plaques, wire injury, compromised collateral vessels, damaged runoff, and compromised bypass target arteries. In addition, progression of tissue loss following failed or haemodynamically insufficient endovascular interventions may result in loss of an optimal window for limb salvage. It is also possible that ENDO failure may be a marker for a higher risk patient or disease patterns.[9] Previous data on the topic have had heterogenous conclusions. The prospective data from the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial showed improved amputation free survival.[13] This was also shown in two Vascular Study Group of New England (VSGNE) analyses.[14,15] However, there are other registries and single centre analyses showing that secondary bypass (SB) is not associated with worse outcomes.[16–19]

This study aimed to compare above ankle amputation rates in patients with CLTI treated with primary infrainguinal bypass (PB) with those treated with a secondary bypass (SB) after initial ENDO. Data from the Best Endovascular versus Best Surgical Therapy in Patients with CLTI (BEST-CLI) randomised trial were queried, which demonstrated that infrainguinal bypass with single segment great saphenous vein (SSGSV) was associated with lower major adverse limb events (MALE) or death compared with ENDO.[3]

MATERIALS AND METHODS

The BEST-CLI trial (NCT02060630) was a multicentre, international, prospective, randomised controlled trial comparing infrainguinal bypass and ENDO in patients with CLTI and infrainguinal peripheral artery disease who were candidates for both revascularisation strategies. This trial had two parallel cohorts based on whether SSGSV was (cohort 1) or was not (cohort 2) available. The availability of conduit was based on the pre-operative vein mapping as interpreted by the investigators at each site. Re-interventions were determined by the treating investigators, with major re-interventions being independently adjudicated for the analysis. The primary outcome of the trial was MALE or death. Details of the trial have previously been described.[3] Primary bypass was defined as infrainguinal bypass performed after initial randomisation within the trial. Secondary bypass was defined as an infrainguinal bypass performed in patients who were initially treated with ENDO and then went on to have a subsequent bypass on the same limb. Primary bypass was compared with SB after index ENDO in all patients and separately within cohorts 1 and 2. Secondary bypass outcomes were also analysed based on whether or not there was initial ENDO technical success. Secondary bypass was also analysed according to timing: early SB was defined as being performed within 30 days of ENDO, while late SB was defined as being performed beyond 30 days. The primary outcome was above ankle amputation with death as a competing risk. The secondary outcome was above ankle amputation and/or all cause death.[14] The institutional review board of each participating institution approved the protocol and the consent process. All subjects gave informed consent before enrolment.

Statistical analyses

Bypass and ENDO comparison was performed using the as treated (patients received the treatment indicated and not by intention to treat) dataset. Characteristics were recorded as mean ± SD for continuous and proportions for categorical variables. Analysed variables included age, gender, congestive heart failure, chronic obstructive pulmonary disease, smoking (current/within past year, more than one year ago, never), chronic kidney disease, end stage kidney disease (ESKD), diabetes mellitus, hypertension, previous myocardial infarction, coronary artery disease, prior stroke/transient ischaemic attack, prior coronary artery bypass graft or percutaneous coronary intervention, ambulatory status (ambulatory without assistance, ambulatory with assistance, non-ambulatory), serum albumin levels, medications, and home living status. Limb and operative details were also recorded.

The associations of baseline characteristics with PB *vs*. SB were analysed. The PB and SB in cohorts 1 and 2 were analysed together and as stratified analyses. Risk adjusted analysis was only planned for cohort 1, as this is where SSGSV was believed to be available before intervention. Continuous variables were compared using Student *t* tests. A univariate linear regression model was fitted for each baseline characteristic. Parameter estimates with 95% confidence intervals (CI) are presented. Multivariable Cox proportional hazards analysis was performed in cohort 1 and included adjustment for age, gender, Wound Ischaemia foot Infection (WIfI) stage, randomisation strata, diabetes mellitus, ESKD, previous index infrainguinal reconstruction, and smoking history, as these were the variables used for the initial BEST-CLI analysis. For above ankle amputation, a sensitivity analysis was performed using competing risk with all cause death as the competing event. Cause specific Cox proportional hazard regression

and Fine–Gray models were used to estimate the cause specific hazard ratio and sub distribution hazards, respectively. In cohort 1, a secondary adjusted analysis was performed using propensity matched data. Age, gender, race, WIFI stage, randomisation strata, diabetes, end stage renal disease, previous index infrainguinal reconstruction, and smoking status were used for estimating the propensity scores. A 3:1 ratio within a calliper width of 0.2 of the standard deviation of the logit of the propensity score was used. For each analysis, $p < .050$ was statistically significant. SAS version 9.4 (SAS Institute, Cary, NC, USA) software was used to conduct the statistical analyses.

RESULTS

Demographics and comorbidities – primary and secondary bypass procedures

A total of 1 665 PB and 158 SB were performed in cohort 1; there were 192 PB and 45 SB in cohort 2. Demographics, comorbidities, and medications were similar between PB and SB in cohort 1, aside from patients in the SB group having higher serum albumin levels (3.7 *vs.* 3.5 g/dL; $p = .041$). There were no major baseline differences between PB and SB groups in cohort 2 (Table 1).

Limb and procedural details – primary and secondary bypass procedures

The PB and SB patients in cohort 1 differed in their baseline WIfI stage distribution, with SB having a lower proportion of both WIfI stage 1 (0.7% *vs.* 7.3%) and stage 4 patients (30.6% *vs.* 37.8%) ($p = .003$). Primary bypass was performed using SSGSV in 87.8% and 19.8% of patients in cohorts 1 and 2, respectively. The PB targets were infrapopliteal in 56% and 49.2% in cohorts 1 and 2, respectively. Among those patients who underwent SB, the index ENDO intervention included the infrapopliteal segment in 27.8% and 35.6% in cohorts 1 and 2, respectively. Among those patients who were initially treated with ENDO and went on to require a SB, the initial ENDO was technically unsuccessful in 49.7% and 57.8% for cohorts 1 and 2, respectively (Table 2).

Time to SB after ENDO occurred at a median of 28 days in all patients and median of 210 days in those who had a successful initial ENDO procedure. In cohort 1, unadjusted 1 year Kaplan–Meier analysis revealed that compared with PB, SB was associated with increased above

ankle amputation (14% *vs*. 8.1%; $p = .002$) (Fig. 1). This remained true when above ankle amputation was analysed with death as a competing risk (13.5 *vs*. 7.4%; $p = .003$). There was no statistically significant difference in the unadjusted amputation rates in cohort 2 (15.9% *vs*. 10.9%; $p = .28$) (Table 3). Composite amputation/death comparing PB with SB was similar overall and in each cohort (Table 3).

The findings in cohort 1 were confirmed on multivariable analysis, where SB was strongly associated with increased above ankle amputation compared with PB (HR 1.72, 95% CI 1.07 – 2.74; $p = .02$). Above ankle amputation remained worse for SB patients when the analysis was restricted to SB performed after a technically successful index ENDO (HR 2.21, 95% CI 1.26 – 3.86; $p = .005$). Risk adjusted analysis of patients having SB after non-technically successfully ENDO showed that outcomes were similar (HR 1.28, 95% CI 0.62 – 2.65; $p = .50$). In cohort 1, results were similar on propensity matched analyses (Table 4) (Supplementary Table S1).

When comparing early SB (within 30 days) and late (> 30 days) SB, the risk of above ankle amputation at one year was 17.7% for early SB, 10.1% for late SB, in comparison with 8.1% for PB. On multivariable risk adjusted analysis of both cohorts 1 and 2, early SB was associated with higher amputation risk (HR 2.01, 95% CI 1.22 – 3.31; $p = .006$). Late SB was not associated with increased amputation risk (HR 1.33, 95% CI 0.78 – 2.27; $p = .29$) (Table 5). When examining pre-operative and index procedural details for patients treated with SB, in both cohorts, above ankle amputation was associated with male gender, impaired ambulatory status, low serum albumin levels, and index ENDO performed on superficial femoral and popliteal arteries (Supplementary Table S2).

DISCUSSION

Using the BEST-CLI multicentre trial dataset, this study demonstrated that SB was associated with a greater incidence of above ankle amputation in comparison with PB among patients who had an adequate SSGSV available at study entry. There was no difference in the composite outcome of above ankle amputation or all cause death, likely due to survival bias that required participants to be alive and fit enough to undergo an SB. These results also held true when analysis was restricted to patients who had an initial technically successful ENDO revascularisation, excluding those with early ENDO failures. Early (within 30 days of the index ENDO) SB was associated with worse outcomes than late SB.

These findings reinforce that an all primary endovascular intervention approach is not a free pass. This holds true even if there is a technically successful initial endovascular intervention where SB is also associated with major amputation. Several prior studies have examined the outcomes of SB after failed ENDO, although they were mostly retrospective and limited to single centre reviews. Results have been mixed, with some data suggesting that endovascular interventions can negatively affect a subsequent infrainguinal bypass. Prospective data from the BASIL trial were used to compare clinical outcomes following PB and SB. There were 190 PB and 49 SB in the BASIL analysis. Primary bypass was associated with a statistically significantly higher amputation free survival rate (PB 60% *vs*. SB 40%) at a median of seven years.[13] A VSGNE analysis of 1 880 bypasses also examined those with prior ENDO. At one year, major amputation and graft occlusion were statistically significantly higher in

patients who received prior ENDO, and this association persisted on risk adjusted analysis.[14] A subsequent VSGNE analysis compared 2 350 PB to 1 154 patients who underwent SB from 2003 – 2011. Over the study period, SBs increased in frequency from 22% to 38% of all bypasses performed. These investigators found that SB was associated with higher MALE and worse re-intervention/amputation free survival compared with PB.[15]

One group reported their experience of endovascular interventions in 604 patients; 33% were for CLTI. Subsequent bypass was performed in 5.3% at a median of 15 months. Blinded adjudication showed that the location of the distal anastomosis changed to a more distal target in 43%, with 27% requiring an infrapopliteal target.[8] Another single centre analysis of 122 patients requiring pedal bypass examined those with prior endovascular interventions. The more distal plantar artery was the more common target in those with previous endovascular re-interventions. Previous endovascular intervention was independently associated with primary patency loss; however, this did not translate into a difference in primary assisted patency, secondary patency, or wound healing.[16]

There are data that suggest that SB after previous endovascular intervention is not associated with increased risk of complications or failure. The Limb-threatening IschaeMia with infragenicular Bypass adopting in situ SAphenous VEin technique (LIMBSAVE) registry enrolled 541 patients with CLTI from 43 centres in Italy. An analysis of 460 of these patients examined 74.1% with PB and 25.9% with bypass after endovascular intervention. At the two year follow up, there were no differences in primary patency, primary assisted patency, and secondary patency between groups.[17] A single centre analysis examined patients who underwent

182 spliced vein bypass procedures, mostly infrapopliteal, after prior endovascular interventions (23%). There were no differences in major amputation rate or patency between primary bypass and bypass after endovascular intervention.[18] Another retrospective review of 314 consecutive autologous vein bypasses (83% great saphenous vein) performed in patients with CLTI included 19% of patients who had a previous endovascular intervention. There were similar one and three year primary patency and amputation free survival rates in patients treated with primary and secondary bypass.[19]

There have been two meta-analyses published on this topic, with contradictory results. One published in 2019 examined 15 studies inclusive of 11 886 patients. At one year, amputation-free survival and primary patency were worse in patients who had a SB.[20] However, another meta-analysis in 2023 analysed 8 064 patients and did not identify a difference in primary patency, amputation, or amputation-free survival at six months, one year, or two years.[11]

This analysis had multiple limitations. The BEST-CLI trial was not powered for SB outcomes. Survival bias may have favoured those selected to undergo SB. Details about the mode of PB failure, or the anatomy and conduit for SB were not collected. There was also a selection bias built in to BEST-CLI, as the investigators had to believe that there was equipoise for both initial bypass and ENDO interventions based upon the affected limb severity, among other factors. Although this paper focused on SB after ENDO, there were still questions about ENDO after bypass. However, BEST-CLI was not designed to provide granular details for ENDO (such as bypass intervention or native circulation) after bypass and unfortunately this analysis could not be performed. Subgroup analyses with non-significant results such as cohort 2

and late bypass were limited by smaller numbers and these may have reflected as being underpowered. Finally, the interventionalists in the BEST-CLI trial used their preferred techniques, creating procedural heterogeneity. The primary outcome of the BEST-CLI trial (MALE or all cause death) was not used in this analysis since SB, by definition, constitutes a MALE event.

Conclusions

In patients with CLTI who were deemed suitable for either infrainguinal bypass or ENDO, SB was associated with statistically significantly worse limb salvage compared with PB, particularly in patients with available SSGSV. These findings suggest that failure of an initial revascularisation can have dire consequences for some patients with CLTI, even in the context of a clinical trial with protocol mandated surveillance and medical management.

CONFLICT OF INTEREST

JS: education grant WL Gore and BD. MM: Janssen – scientific advisory board. MC: Abbott Vascular DSMB. KR: member of the Scientific Advisory Board or Consultant for Abbott Vascular, Access Vascular, Boston Scientific-BTG, Volcano-Philips, Surmodics, Cruzar Systems, Magneto, Summa Therapeutics, and University of Maryland; an unpaid member of the Scientific Advisory Board of Thrombolex, Inc; received grants from NIH and Boston Scientific; has equity from Access Vascular, Accolade, Contego, Endospan, Embolitech, Eximo, JanaCare, PQ Bypass, Primacea, MD Insider, Shockwave, Silk Road, Summa Therapeutics, Cruzar

Systems, Capture Vascular, Magneto, Micell, and Valcare; and is a board member of VIVA Physicians, a not-for-profit 501c3, and National PERT Consortium, a not for profit 501c3.

AF: Novo Nordisk Foundation, Grant recipient; Sanifit, Consultant; LeMaitre, Consultant; BioGenCell, 11 Consultant; Dialysis-X, Advisory Board; iThera Medical, Advisory Board.

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REFERENCES

1. Siracuse JJ, Menard MT, Eslami MH, Kalish JA, Robinson WP, Eberhardt RT, et al. Comparison of open and endovascular treatment of patients with critical limb ischemia in the Vascular Quality Initiative. *J Vasc Surg* 2016;**63**:958–65.e1.
2. Gallagher KA, Meltzer AJ, Ravin RA, Graham A, Shrikhande G, Connolly PH, et al. Endovascular management as first therapy for chronic total occlusion of the lower extremity arteries: comparison of balloon angioplasty, stenting, and directional atherectomy. *J Endovasc Ther* 2011;**18**:624–37.
3. Farber A, Menard MT, Conte MS, Kaufman JA, Powell RJ, Choudhry NK, et al. Surgery or endovascular therapy for chronic limb-threatening ischemia. *N Engl J Med* 2022;**387**:2305–16.
4. Bradbury AW, Moakes CA, Popplewell M, Meecham L, Bate GR, Kelly L, et al. A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial. *Lancet* 2023;**401**:1798–809.
5. Zarrintan S, Rahgozar S, Ross EG, Farber A, Menard MT, Conte MS, et al. Endovascular therapy versus bypass for chronic limb-threatening ischemia in a real-world practice. *J Vasc Surg* 2024;**80**:1169–81.

6. Giles KA, Farber A, Menard MT, Conte MS, Nolan BW, Siracuse JJ, et al. Surgery or endovascular therapy for patients with chronic limb-threatening ischemia requiring infrapopliteal interventions. *J Vasc Surg* 2024;**80**:1515–24.

7. Abu Dabrh AM, Steffen MW, Asi N, Undavalli C, Wang Z, Elamin MB, et. Bypass surgery versus endovascular interventions in severe or critical limb ischemia. *J Vasc Surg* 2016;**63**:244–53.e11.

8. Gifford SM, Fleming MD, Mendes BC, Stauffer KC, De Martino RR, Oderich GS, et al. Impact of femoropopliteal endovascular interventions on subsequent open bypass. *J Vasc Surg* 2016;**64**:623–8.

9. Roy T, Forbes T, Wright G, Dueck A. Burning bridges: mechanisms and implications of endovascular failure in the treatment of peripheral artery disease. *J Endovasc Ther* 2015;**22**:874–80.

10. Spinelli F, Pipitò N, Martelli E, Benedetto F, De Caridi G, Spinelli D, et al. Endo first is not appropriate in some patients with critical limb ischemia because "bridges are burned". *Ann Vasc Surg* 2015;**29**:272–7.

11. Yu X, Wang B, Qiu C, He Y, Chen T, Zhu Q, et al. A systematic review and meta-analysis of primary bypass surgery compared with bypass surgery after endovascular treatment in peripheral artery disease patients. *J Vasc Surg* 2023;**78**:1335–45.e4.

12. Sandford RM, Bown MJ, Sayers RD, London JN, Naylor AR, McCarthy MJ. Is infrainguinal bypass grafting successful following failed angioplasty? *Eur J Vasc Endovasc Surg* 2007;**34**:29–34.

13. Meecham L, Patel S, Bate GR, Bradbury AW. A comparison of clinical outcomes between primary bypass and secondary bypass after failed plain balloon angioplasty in the Bypass versus Angioplasty for Severe Ischaemia of the Limb (BASIL) trial. *Eur J Vasc Endovasc Surg* 2018;**55**:666–71.

14. Nolan BW, De Martino RR, Stone DH, Schanzer A, Goodney PP, Walsh DW, et al. Prior failed ipsilateral percutaneous endovascular intervention in patients with critical limb ischemia predicts poor outcome after lower extremity bypass. *J Vasc Surg* 2011;**54**:730–5; discussion 735–6.

15. Jones DW, Schanzer A, Zhao Y, MacKenzie TA, Nolan BW, Conte MS, et al. Growing impact of restenosis on the surgical treatment of peripheral arterial disease. *J Am Heart Assoc* 2013;**2**:e000345

16. Mohapatra A, Lowenkamp MN, Henry JC, Boitet A, Avgerinos ED, Chaer RA, et al. Prior endovascular intervention is not detrimental to pedal bypasses for ischemic wounds. *Ann Vasc Surg* 2018;**50**:80–7.

17. Troisi N, Michelagnoli S, Adami D, Berchiolli R; LIMBSAVE registry Collaborative Group. Comparison of long occlusive femoropopliteal de novo versus previous

endovascularly treated lesions managed with in situ saphenous bypass. *J Vasc Surg* 2022;**76**:797–805.

18. Ramdon A, Lee D, Hnath JC, Chang B, Feustel PJ, Darling RC 3rd. Effects of endovascular first strategy on spliced vein bypass outcomes. *J Vasc Surg* 2020;**71**:880–8.

19. Santo VJ, Dargon P, Azarbal AF, Liem TK, Mitchell EL, Landry GJ, et al. Lower extremity autologous vein bypass for critical limb ischemia is not adversely affected by prior endovascular procedure. *J Vasc Surg* 2014;**60**:129–35.

20. Hossain S, Leblanc D, Farber A, Power AH, DeRose G, Duncan A, et al. Infrainguinal bypass following failed endovascular intervention compared with primary bypass: a systematic review and meta-analysis. *Eur J Vasc Endovasc Surg* 2019;**57**:382–91.

Table 1. Baseline characteristics for primary and secondary bypass after endovascular intervention in as treated dataset.

	Cohort 1			Cohort 2		
Characteristics	**Primary bypass (*n* = 665)**	**Secondary bypass (*n* = 158)**	***p* value**	**Primary bypass (*n* = 192)**	**Secondary bypass (*n* = 45)**	***p* value**
Demographics						
Age – y	66.7 ± 9.6	65.8 ± 10	.29	68.3 ± 8.7	69.5 ± 10.4	.42
Male gender	72.2	74.1	.64	72.9	75.6	.72
Hispanic	11.6	8.9	.33	15.1	8.9	.28
Comorbidities						
Obese	35.6	31.8	.37	25.4	31.7	.41
Hypertension	86.6	86.1	.87	86.5	95.6	.089
Previous MI	48.7	51.4	.69	54.6	60.9	.59
Prior CABG	39.1	43.2	.51	69.1	52.2	.12
Prior PCI	40.5	39.2	.84	30.9	43.5	.25
CHF	5	5.7	.72	6.3	6.7	.92
COPD	14	16.5	.44	17.2	24.4	.26
Prior TIA/stroke	13.7	17.1	.28	22.9	17.8	.45
Chronic kidney disease	26.1	24.7	.72	23.4	26.7	.65
ESKD	8.9	10.1	.63	12	8.9	.56
Smoking, never	21.1	17.7	.22	20.8	11.1	.19
Smoking, prior	33.3	29.1		34.4	46.7	

Smoking, current	45.6	53.2		44.8	42.2	
Diabetes mellitus	71.8	66.5	.19	62	46.7	.06
Ambulatory without assistance	55.3	60.1	.48	56.3	62.2	.11
Ambulatory with assistance	33.4	31		33.9	20.0	
Non-ambulatory	11.3	8.9		9.9	17.8	
Living at home	95.6	94.9	.71	95.8	91.1	.19
Serum albumin	3.5 ± 0.6	3.7 ± 0.6	.04	3.6 ± 0.7	3.5 ± 0.7	.92
Medications						
Statin	70.7	71.5	.83	78.1	75.6	.71
Single antiplatelet	57.4	57.6	.9	58.3	57.8	.71
Anticoagulant	10.2	8.9	.61	10.9	17.8	.21

Dara are presented as % and mean ± SD. MI = myocardial infarction; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; TIA = transient ischaemic attack; ESKD = end stage kidney disease.

Table 2. Limb and procedural details for primary and secondary bypass after endovascular intervention in the as treated dataset.

	Cohort 1			Cohort 2		
Characteristics	**Primary bypass (*n* = 665)**	**Secondary bypass (*n* = 158)**	***p* value**	**Primary bypass (*n* = 192)**	**Secondary bypass (*n* = 45)**	***p* value**
Limb details						
Prior revascularisation	5.7	4.4	.52	9.9	15.6	.28
WIfI stage 1	7.3	0.7	.003	5.4	2.5	.85
WIfI stage 2	27.3	31.9		36.1	40	
WIfI stage 3	27.6	36.8		27.7	25	
WIfI stage 4	37.8	30.6		30.7	32.5	
Ankle–brachial index	0.6 ± 0.3	0.6 ± 0.3	.66	0.5 ± 0.3	0.5 ± .4	.99
Toe pressure	35.4 ± 25.0	30.3 ± 18.9	.14	36.0 ± 23.7	25.2 ± 21.1	.057
Index bypass details						
Bypass using SSGSV	87.8			19.8		
Index endovascular details						
SFA		52.5			40.0	
Popliteal		44.3			42.2	

Infrapopliteal		27.8		35.6	
Multilevel		20.3		31.1	
Any atherectomy		9.5		8.9	
Any stent		36.7		33.3	
Bypass level treated			.004		.44
Femoropopliteal	44.1	60.7	50.8	40.7	
Infrapopliteal	17.8	10.7	10.3	7.4	
Femoropopliteal + infrapopliteal	38.2	28.6	38.9	51.9	
Endovascular technical success		50.3		42.2	

Data are presented as % and mean ± SD. WIfI = wound, ischaemia, foot infection; SSGSV = single segment great saphenous vein; SFA = superficial femoral artery.

Table 3. Kaplan–Meier analysis of unadjusted outcomes at 1 year for primary *vs*. secondary bypass in the as treated dataset.

Outcomes	Primary bypass	Secondary bypass	*p* value
All cohorts			
Above ankle amputation	8.55	14.4	.006
Above ankle amputation analysed with death as competing risk	8.1	14	.002
Amputation or all cause death	19.1	17.5	.59
Cohort 1			
Above ankle amputation	7.7	13.9	.008
Above ankle amputation analysed with death as competing risk	7.4	13.5	.003
Amputation or all cause death	16.8	17.3	.88
Cohort 2			
Above ankle amputation	11.8	16.2	.48
Above ankle amputation analysed with death as competing risk	10.9	15.9	.28
Amputation or all cause death	27.9	18.3	.31

Data are presented as %.

Table 4. Adjusted analyses comparing secondary bypass after endovascular interventions with primary bypass in cohort 1 in the as treated dataset.

Outcome	HR	95% CI	*P* value
Above ankle amputation			
Multivariable	1.72	1.08–2.73	.02
Propensity matched	1.62	1.04–2.54	.034
Above ankle amputation – ENDO technical success only			
Multivariable	2.21	1.26–3.86	.005
Propensity matched	3.1	1.74–5.54	<.001

HR = hazard ratio; CI = confidence interval; ENDO = endovascular intervention.

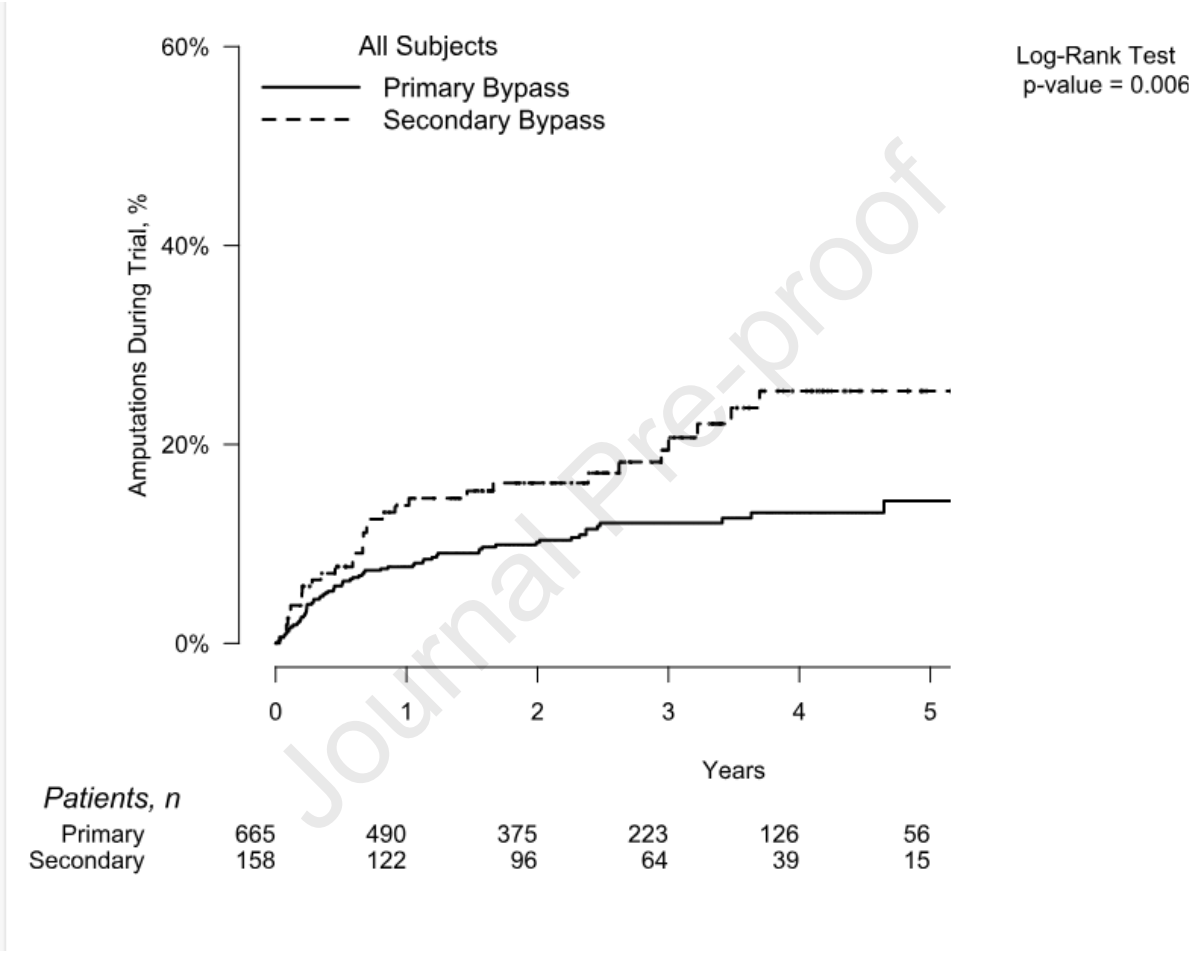
Table 5. Association with early and late secondary bypass after endovascular interventions with above ankle amputation for both cohorts 1 and 2 in the as treated dataset.

Covariate (effect)	HR	95% CI	*p* value
Early secondary *vs*. primary bypass	2.01	1.22–3.31	.006
Late secondary *vs*. primary bypass	1.33	0.78–2.27	.29
Cohort 2 *vs*. 1	1.83	1.2–2.81	.005
Female gender	0.55	0.34–0.9	.018
Age – y	0.97	0.95–0.99	.004
Diabetes	1.06	0.67–1.67	.81
ESKD	1.14	0.64–2.1	.65
Previous revascularisation of index limb	1.15	0.61–2.18	.67
Smoking prior, >1 year	0.98	0.55–1.72	.93
Smoking prior, 2 weeks to 1 year	0.95	0.45–2.17	.91
Smoking current *vs*. never	1.06	0.59–1.89	.85
Stratum 2	1.15	0.46–2.83	.77
Stratum 3	0.91	0.38–2.21	.84
Stratum 4	1.39	0.58–3.35	.47
WIfI stage 2	1.71	0.5–5.85	.39
WIfI stage 3	2.16	0.6–7.86	.24

WIfI stage 4	2.48	0.7–8.65	.16

ESKD = end stage kidney disease; WIfI = wound, ischaemia, foot infection; HR = hazard ratio; CI = confidence interval.

Figure 1. Cumulative Kaplan–Meier analysis of amputations during the BEST-CLI trial stratified by patients undergoing primary *vs*. secondary bypass in cohort 1.



Typesetter instructions

Supplementary Table S1. Baseline characteristics after propensity matching in cohort 1 in the as treated dataset.

Supplementary Table S2. Details for secondary bypass comparing those with and without above ankle amputation in both cohorts 1 and 2 in the as treated dataset.

Figure 1. Cumulative Kaplan–Meier analysis of amputations during the BEST-CLI trial stratified by patients undergoing primary *vs*. secondary bypass in cohort 1.

Please use sentence case: All subjects, Primary bypass, Secondary bypass, Log rank test
Amend p-value = 0.006 to *p* = .006
y-axis label: Amputations during trail – %
Remove % after all numbers on y-axis: 60 not 60%