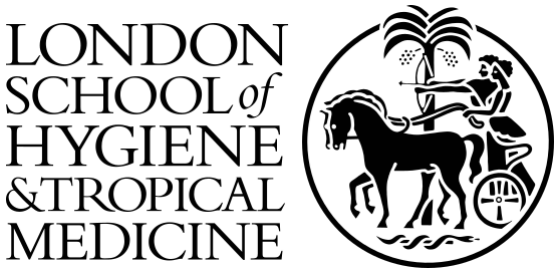

British Journal of Surgery

BJS

Risk of Major Lower Limb Amputation and Death Following Endovascular and Open Revascularisation: A Population-based Study in England

Journal:	*British Journal of Surgery*
Manuscript ID	BJS-0276-Feb-17.R4
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	n/a
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Keywords:	revascularisation, major amputation, death, Hospital Episode Statistics, peripheral arterial disease

Risk of Major Lower Limb Amputation and Death Following Endovascular and Open Revascularisation: A Population-based Study in England

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Funding

This study was undertaken as part of the work by the National Vascular Registry to evaluate the clinical outcomes achieved by English NHS vascular units. The National Vascular Registry is commissioned by the Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit Programme (NCAPOP). The funding bodies had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Category: original article

Based on a previous communication to a society or a meeting: No.

Abstract

Aim

The aim of this investigation was to estimate separate risks of major lower limb amputation and death following revascularisation for peripheral artery disease (PAD) using competing risks analysis.

Methods

Routinely collected data from Hospital Episode Statistics (HES) were used to identify patients who underwent endovascular or open lower limb revascularisation in England in 2005-2015. The primary outcomes were major lower limb amputation and death within 5 years of revascularisation. Cox proportional hazards and Fine-Gray competing risks regression were used to examine the competing risks of these outcomes.

Results

Some 164 845 patients underwent their first lower limb revascularisation for PAD in 2005-2015. Most patients were men (64.6%); the median age was 71 years (IQR: 62- 78 years). Following endovascular revascularisation, the 5-year cumulative incidence of amputation was 4.2% in patients with intermittent claudication and 18.0% in those with a record of tissue loss. After open revascularisation, the corresponding rates were 10.7% and 25.3% and after combined procedures, they were 8.1% and 25.0%. The 5-year cumulative incidence of death varied from 24.6% to 40.3%, depending on procedure type. Competing risks methods consistently produced lower estimates than standard methods.

Conclusion

Our findings suggest that the 5-year risk of major amputation following lower limb revascularisation for PAD is lower than previously estimated. Patients undergoing revascularisation for tissue loss and those who need open revascularisation are at highest risk of limb loss.

Comment [U1]: Are the data in the results presented above based on competing risk models?

Our response: Yes, all result s in the abstract are based on compering risks analyses.

Introduction

Peripheral artery disease (PAD), characterised by atherosclerosis in the arteries of the extremities, is the third most common cause of morbidity worldwide, after stroke and coronary heart disease.[1] The prevalence of PAD is growing: in 2010, an estimated 61 million men and women in high-income countries were living with this disease, representing a 13% increase during the preceding decade.[1] An important treatment goal in PAD is to manage blood flow to the limb. Where medical treatment or lifestyle modification have been inadequate, endovascular and open revascularisation procedures can be used to improve the blood flow. These interventions carry appreciable risks to life and limb.[2, 3] In the Bypass versus Angioplasty for Severe Ischaemia of the Limb (BASIL) study, a multi-centre trial conducted in 27 United Kingdom hospitals in 1999-2004, the investigators reported 3-year rates of amputation-free survival of 57% among patients randomised to bypass and 52% among those randomised to angioplasty. [2] Register-based studies conducted in the United States and Sweden between 1996 and 2003 have shown similar findings, with 5-year rates of amputation-free survival following leg bypass reported as just under 50%. [4, 5]

Previous studies of patient outcomes following lower limb revascularisation have reported on death or amputation-free survival (time to death or major lower limb amputation, whichever occurs first) [2-6]. Few investigations have provided information on the risk of amputation independently of the risk of death, although this is an important outcome for patients. In studies that have reported separate amputation rates, time to amputation has typically been derived using standard Kaplan-Meier analysis and Cox proportional hazards regression. [4, 7-9] These methods are based on the assumption that the risks of multiple outcomes are independent, and they will produce biased estimates in the presence of non-independent, competing risks [10, 11]. The independent risks-assumption is unlikely to be valid in a population of patients undergoing revascularisation for PAD. In this group of typically older patients with high level of multimorbidity, rates of both death and amputation are relatively high, and the rate of amputation is influenced by the rate of death. This is because patients who have died are no longer at risk of having an amputation, and the risks of amputation and death are therefore not independent of one another. It is thus likely that many previously published estimates of the risk of amputation following lower limb revascularisation have been overestimated by standard methods, and more accurate estimates are needed.

To address this gap in the knowledge, the aim of the current investigation was to examine the separate risks of major lower limb amputation and death following endovascular and open lower limb revascularisation procedures undertaken in England between January 2005 and December 2015, using a competing risks approach [12].

Methods

Data sources

Individual-level data were used to identify all lower limb revascularisation procedures due to PAD recorded in Hospital Episode Statistics (HES), an administrative dataset containing information on all hospital admissions in National Health Service (NHS) hospitals in England [13]. Patient HES records include information on procedures, patient characteristics and admission details. Medical diagnoses are coded using the International Classification of Diseases (ICD, version 10) and procedures using the Office of Population, Census and Surveys (OPCS, version 4) codes. In the analyses described here, each patient was identified using an anonymised label, which allowed all of his or her admissions data to be linked. Patient deaths were ascertained from Office for National Statistics (ONS) records of deaths registered in England up to December 2015 [14].

Study population

The study population comprised men and women, aged 35 years or older, who underwent their first lower limb revascularisation for PAD (index procedure) between 1st January 2005 and 31st December 2015. Patients who had a HES record of a lower limb revascularisation up to three years prior to the index procedure were excluded. Further excluded were non-UK residents, patients whose primary indication for revascularisation was malignant or benign neoplastic disease, trauma or congenital malformation, and those with incomplete data on covariates (<0.01%).

Revascularisation procedures were grouped into three categories: endovascular revascularisation alone, open revascularisation (endarterectomy, profundaplasty or bypass) alone, or a combination endovascular and open procedures. Primary and secondary diagnostic codes at the index admission were used to identify patients undergoing these procedures for PAD. Patients were categorised into groups indicating increasing severity of PAD as follows: intermittent claudication (IC: ICD-10 code I73.9 for intermittent claudication), severe limb ischaemia without a record of tissue loss (SLI: ICD-10 code(s) I70.2, I72.4, I70.0-8, I74.3-5,

I77.1 or I77.9 but no code(s) for diabetes with peripheral circulatory complications or tissue loss) and severe limb ischaemia with a record tissue loss (TL: code(s) for PAD and code(s) indicating tissue loss or diabetes with peripheral circulatory complications). The OPCS and ICD-10 codes used to identify the revascularisation procedures and indications are provided in the Online Appendix, Supplementary Tables S1-S3.

Comment [kh2]: Added explanation on how HES codes were used to define categories.

The risk estimates were adjusted for patient age, sex and the RCS Charlson score, which was derived using primary and secondary diagnostic codes from the index hospital admission as well as admissions during the 12 months preceding the index admission.[15] Acute conditions (e.g. myocardial infarction) were included in the number of co-morbidities only if they were present in a record of a hospital admission preceding the index admission. (Online Appendix, Supplementary Table S4). PAD and diabetes were excluded from the calculation of the comorbidity score because these formed part of the inclusion criteria for the study, and all patients had a record of at least one of these.

Outcomes

The primary outcomes were major lower limb (i.e. above the ankle) amputation (ipsilateral or contralateral) and death from any cause, on a date later than the date of the revascularisation procedure. Amputations due to trauma or neoplastic disease were excluded. Amputation-free survival (time from revascularisation procedure to major amputation, death from any cause or the end of follow-up, whichever occurred first) was examined as a secondary outcome. OPCS codes for identifying major lower limb amputations are provided in Online Appendix, Supplementary Table S5.

Statistical analyses

Patients were followed up from the date of the revascularisation to the date of a subsequent major lower-limb amputation, death or the end of follow-up (December 2015), for a maximum of 5 years. The cumulative incidences of major amputation and death, independently from one another, were estimated for each type of revascularisation and indication for treatment using Fine-Gray competing risks regression models [12]. The competing risks approach was chosen because in the presence of non-independent, competing risks, the cumulative incidence of an outcome (such as major amputation) is influenced by the cumulative incidence(s) of competing outcome(s) (such as death) [10, 11]. The Fine-Gray model overcomes this problem by producing separate estimates for the cumulative incidence

of the main outcome and the competing outcome.[12] Using the competing risks approach, amputation-free survival was calculated as one minus the sum of the independent cumulative incidences of amputation and death.

Three sensitivity analyses were conducted: the first one used Kaplan-Meier curves and Cox proportional hazards regression [16] to illustrate the degree to which the risk of amputation is overestimated using standard survival analysis methods, the second one examined the impact of not adjusting for the RCS Charlson score in the competing risks models and the third investigated the effect of combining SLI and TL as one analytical category. The latter two analyses were done to explore the impact of the quality of coding for secondary diagnoses and comorbidities in HES).

Comment [kh3]: Added a sensitivity analysis.

Proportional hazards assumption for the Cox models was checked visually, using log-log-plots (of log-log of the survival function against the logarithm of time) and Schoenfeld test (testing for interaction between Schoenfeld residuals and time). In the competing risk models the proportionality of sub-distribution hazards was checked by including in the model an interaction term with time. The assumptions were reasonably valid for all procedure-outcome pairs. Age (ten-year bands from 30 to 80+), sex, the RCS Charlson score (0, 1, 2, 3+), and indication for revascularisation (IC, SLI or TL) were modelled as categorical variables. All analyses were conducted using Stata MP 14 (Stata Corporation, College Station, Texas, US).

Results

Between January 2005 and December 2015, some 164 845 men and women underwent their first lower limb revascularisation for PAD. Overall, the majority of these patients were men (64.6%) and the median age was 72 years (interquartile range, IQR: 62 to 78 years). The most common procedure was endovascular revascularisation alone (n=120 463, 73% of the procedures), followed by open revascularisation alone (n=39 824, 24%) and endovascular and open procedures together (n=4 558, 3%).

Severe limb ischaemia (SLI) without record of tissue loss was the most common indication for endovascular revascularisation, recorded as the underlying aetiology in 55.6% of all revascularisation procedures. IC was the indication for 23.9% of the patients in all procedure groups and severe limb ischaemia with a record of tissue loss (TL) accounted for 21.6%

(Table 1). Overall, around 86% of patients had at least one comorbidity indicated by the RCS Charlson score, and 22% of patients had three or more.

In all, 13 620 patients (8.3%) underwent a major lower limb amputation and 42 570 (25.8%) died during the 5 years following lower limb revascularisation. Median follow-up was 3 years (IQR: 1 to 5 years). The unadjusted estimates of cumulative incidence of major lower limb amputations associated with each type of revascularisation were calculated using the Kaplan-Meier and Fine-Gray methods (Figure 1). The Kaplan-Meier method consistently produced higher estimates of the risk of amputation, particularly towards longer follow-up, demonstrating that standard methods tend to overestimate the risk of amputation when the competing risk of death is not taken into account in the analyses.

Unadjusted cumulative incidences of amputation and death at 1, 3 and 5 years after revascularisation were calculated using competing risks approach (Table 2). The cumulative incidence of major lower limb amputation was higher in patients undergoing open revascularisation than in those undergoing endovascular procedures. It was also notably higher in patients who underwent revascularisation for limb ischaemia with a record of tissue loss (TL), compared to patients whose indication for revascularisation was intermittent claudication (IC) or severe limb ischaemia without a record of tissue loss (SLI) (Table 2). The cumulative incidence of death was relatively high in all patient groups.

Amputation-free survival, calculated using competing risks methods, is shown by procedure type and indication in Table 3. Amputation-free survival at 5 years varied by procedure type and indication: it was the lowest, 26.1%, in those who underwent endovascular revascularisation for TL and the highest, 71.1%, in those who had endovascular procedures for IC. Amputation-free survival at 5 years following open and combined procedures showed similar patterns. Of patients who underwent open or combined revascularisation for TL about 30% survived, free of major lower limb amputation, at 5 years following revascularisation. Of patients who underwent these procedures for IC, some 60%% survived to 5 years without a major amputation (Table 3).

Cumulative incidences of amputation and death, adjusted for patient age, sex and RCS Charlson score, are shown in Figures 2-4 and Table 4. Overall, the cumulative incidence of both outcomes increased sharply over the first year after revascularisation in all procedure

Comment [U4]: Can you explain to me the difference between
1)SLI
2)SLI with tissue loss
3)IC
The suggestion that 55.2% had SLI (presumably) without tissue loss is improbably high and not consistent with general clinical practice ie most patients with SLI have some form of tissue loss (gangrene / ulcer / minor amputation). Please clarify.

This will confuse readers and make them question the validity of the results.

For comparison please see Mark Nehler and Alan Hirsch's work on CLI at the population level – which confirms that most patients with CLI have either ulceration / gangrene / tissue loss. Fewer have rest pain only.
J Vasc Surg. 2014;60:686-95

Your data also conflict with German national data – published by Holger Reinecke
Eur Heart J. 2015;36:932-8

Our response: please see our earlier comment in this document (last 3 lines of p. 4 and first 3 lines of p. 5) and also our point-by-point response to the Editor's comments.

Comment [kh5]: Noted the overall length of follow-up here.

Comment [kh6]: For transparency, we propose moving Table 4 (previously table S6) from the appendix to the main paper.

and indication groups; for the following years, the increase continued, at a steady but lower rate. At 5 years post-revascularisation, the adjusted cumulative incidence of amputation was the lowest among patients undergoing endovascular procedures for IC (4.2%) and the highest among those having open revascularisation for TL (25.3%) (Figures 2-4; Table 4).

When estimated independently from the cumulative incidence of amputation and adjusted for patient characteristics, the cumulative incidence of death was relatively high in all patient groups: regardless of indication for the intervention, between approximately 25% and 39% of patients died within 5 years of the revascularisation procedure. (Figures 2-4; Table 4 ~~Supplementary Table S6~~).

The results from the sensitivity analyses exploring the potential impact of the quality of diagnostic coding suggest that the main findings of the study are reasonably robust. The results from the analyses without adjustment for the RCS Charlson score were nearly identical to the main findings (Online Appendix, Figures, S1-S3), reflecting the fact that the burden of comorbidity was similar across the indication categories. The risk of amputation in the combined SLI+TL group was elevated compared to the SLI group, as might be expected, but the difference was relatively modest (Table 2). Similarly, amputation-free survival in the SLI+TL group somewhat lower in the SLI group (Table 3). These observations suggest that, while misclassification of patients as having SLI only when in reality they also had tissue loss (something suggested by the large proportion of patients in the SLI category) would inflate the risk estimates for the SLI group, the influence of such bias on the main findings is likely to be small. The sensitivity analysis comparing the two analytical approaches demonstrated that the risks of both amputation and death estimated using Kaplan-Meier methods were higher than those estimated using competing risks methods, particularly among patients with a record of tissue loss (Online Appendix, Figures, S1-S3).

Discussion

Competing risks approach consistently produced lower estimates of the cumulative incidence of both outcomes than did standard survival analysis methods, particularly towards the end of the 5-year follow up and for patients with the most severe PAD (TL).

Findings from previous studies in England, Sweden and the United States suggest that the overall 5-year rates of major lower limb amputation following open and endovascular

revascularisation lie between 40% and 50% [2-5]. The findings presented here suggest that the risk of amputation following revascularisation for PAD is lower: the highest risks of major lower limb amputation, some 25%, were observed in patients undergoing open procedures (either alone or in combination with endovascular revascularisation) for the most severe underlying disease (TL). By contrast, the 5-year risk of amputation was the lowest among patients who underwent endovascular revascularisation for IC or SLI (4% and 7%, respectively). The differences between our observations and those of previous studies are likely to relate to standard survival analysis (Kaplan-Meier and Cox) methods overestimating the risk of amputation in this patient population where the risks of amputation and death are not independent of one another, and where most patients have a high risk of death due to old age and multiple comorbidities.

Amputation-free survival at five years from revascularisation, calculated using competing risks methods, was between 26% and 71% following endovascular procedures and between 30% and 60% after open procedures (either alone or in combination with endovascular revascularisation). However, compared to conservative treatment for limb ischaemia, the outcomes following endovascular and surgical revascularisation are encouraging. Estimates from a recent meta-analysis suggest that at one year of follow-up, over 40% of the patients receiving conservative treatment had lost a limb and about 25% had died.[17]

The overall risk estimates can mask meaningful differences in the risks of outcomes between patients with different severity of underlying disease. The findings from a longitudinal analysis of public health insurance data from over 41 000 German men and women suggest that the 4-year risks of amputation and death vary considerably according to disease severity, ranging from 4.6% in Rutherford category 1 to 67.3% in Rutherford category 6.[9] The observations presented here were similar in direction but smaller in magnitude: the 5-year risks of major lower limb amputation varied from approximately 4.2% in patients undergoing endovascular revascularisation for IC (the least severe disease) to 25.3% in those undergoing open repair for TL (the most severe PAD). Again, one explanation for the discrepancies in the results is likely to be standard survival methods over-estimating risks. However, it must be noted that he findings presented here may not be directly comparable to those from other countries, because the ICD-10 codes in HES data do not allow a conclusive distinction to be made between the categories indicating the severity of PAD. Consequently, the risk estimates relating to IC, SLI and TL patients in the present analyses should be taken as indicative of

typical risks in these patient groups within England, and not directly used in international comparisons.

An important strength of the current investigation is the use of a competing risks approach, which allows the estimation of the risks of amputation and death separately from one another, thus providing accurate estimates of these risks. Furthermore, the analyses were based on prospectively collected individual-patient data on all revascularisations in English NHS hospitals in 2005-2015. Therefore, it is unlikely that the findings reported here have been biased by sample selection or loss to follow-up. Based on information on just under 165 000 patients, the analyses likely have sufficient statistical power to provide precise estimates of the risk of amputation following endovascular and open revascularisation procedures in England.

Despite the strengths of large data, analyses based on administrative hospital data, such as HES, are prone to biases arising from incomplete or inaccurate clinical coding. A systematic review on the data quality in HES data suggests that the accuracy of diagnostic coding was less than satisfactory up to the mid- to late 2000s, but that it has improved since.[18] However, there is evidence that whilst many primary diagnoses and procedures are coded reasonably accurately, [19] the quality of coding for subsequent diagnoses and procedures varies between hospitals.[20] It is therefore possible that the findings of the current investigation have been influenced by differential omission of secondary diagnostic codes and the lack of consistency in coding PAD symptoms using ICD-10. To minimise the effect of coding errors, a wide range of codes was used to capture as many disease events as possible for the purposes of defining the severity of PAD and identifying comorbidities. However, the severity of the underlying PAD and the number of comorbidities (which were based on secondary diagnostic codes) may have been under-ascertained if coding of secondary diagnoses was incomplete or inaccurate. Misclassifying patients to having fewer comorbidities than they in reality had could dilute the cumulative incidence estimates by introducing error (statistical "noise") to them. Similarly, misclassifying more severely ill patients into less severely ill categories could lead to overestimation of the risks of amputation and death for the less severe indication. However, the sensitivity analyses suggest that the potential bias this might have introduced to the SLI group was small. Misclassification in covariates would also reduce the ability to adjust for these [21]. Analyses based on better quality data on patient-level risk factors would help to gauge the extent and impact of these potential biases in administrative data.

Comment [kh7]: Challenges of diagnostic coding to define severity of PAD are discussed here.

It was not possible to reliably ascertain the laterality of the amputations based n HES data, and it is thus not known what proportion of the amputations were done on the same leg as the revascularisation. However, in terms of providing information that is relevant to patients, this is not a major limitation, as patients tend to be concerned about their overall risk of losing a limb after revascularisation, rather than specific risks of losing the ipsilateral or contralateral limb.

Finally, whilst HES is a rich source of data on hospital admissions and procedures, it does not contain data on patient-level physiological or lifestyle factors, which may influence the risk of amputation or death following lower limb revascularisation. For this reason, it was not possible to investigate the potential impact of factors such as smoking, control of blood pressure or diabetes, or physical activity on the present study's findings. These are areas to target in future research.

The findings of this study support those of previous studies that standard survival analysis methods can overestimate the risk of the primary outcome of interest in the presence of a competing outcome [11]. This highlights the importance of using appropriate statistical methods to estimate the risk of amputation in the population undergoing revascularisation, as most of these patients are at high of death due to old age and multiple comorbidities. Importantly, using the appropriate methodology allows accurate detection of variation in clinical outcomes, which is needed for planning of healthcare delivery and resource allocation in vascular surgery and other areas alike.

Supporting information

Online Appendix. Supplementary tables and figures

Disclosure

The authors declare no competing interests.

Acknowledgements

We thank the BJS editor and reviewers for their helpful comments and suggestions for improving the manuscript.

Ethics approval

The study is exempt from UK National Research Ethics Committee approval as it involved secondary analysis of an existing dataset of anonymised data. HES data were made available by the NHS Digital (Copyright© 2015, reused with the permission of NHS Digital. All rights reserved).

Data sharing

The authors do not have permission to share patient-level HES data. HES data are available from the NHS Digital Data Access Advisory Group (enquiries@nhsdigital.nhs.uk) for studies who meet the criteria for access to confidential data.

Preregistration of study

No preregistration exists for the analyses reported in this article.

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Figure legends

Figure 1. Kaplan-Meier and competing risks estimates of cumulative incidence of amputation following lower limb revascularisation

Footnote to figure 1: K-M: Kaplan-Meier estimates; CR: competing risks estimates.

Figure 2. Risk of amputation and death following endovascular revascularisation, by indication

Footnote to Figure 2: Estimates adjusted for age, sex, and RCS Charlson score.

IC: intermittent claudication; SLI: severe limb ischaemia without record of tissue loss; TL: severe limb ischaemia with a record of tissue loss.

Figure 3. Risk of amputation and death following open revascularisation, by indication

Footnote to Figure 3: Estimates adjusted for age, sex, and RCS Charlson score.

IC: intermittent claudication; SLI: severe limb ischaemia without record of tissue loss; TL: severe limb ischaemia with record of tissue loss.

Figure 4. Risk of amputation and death following a combination of endovascular and open revascularisation, by indication

Footnote to Figure 4: Estimates adjusted for age, sex, and RCS Charlson score.

IC: intermittent claudication; SLI: severe limb ischaemia without record of tissue loss; TL: severe limb ischaemia with a record of tissue loss.

Table 1. Characteristics of patients undergoing lower limb revascularisation for peripheral arterial disease (PAD) in 2005-2015

Procedure	**N procedures**	**Men** N (%)	**Age (years)** Median (IQR)	**Indication**[1]	N (%)	**RCS Charlson score** [2]	N (%)
Endovascular	120 463	75 201 (62.4)	71 (62 to 79)	**IC**	26 579 (22.1)	**0**	17 305 (14.4)
				SLI	67 416 (56.0)	**1**	67 208 (55.8)
				TL	26 468 (22.0)	**2**	10 394 (8.6)
						3+	25 556 (21.2)
				SLI+TL	93 884 (78.0)		
Open	39 824	28 076 (70.5)	70 (62 to 78)	**IC**	10 145 (25.5)	**0**	5 736 (14.4)
				SLI	21 580 (54.2)	**1**	20 778 (52.2)
				TL	8 099 (20.3)	**2**	3 895 (9.8)
						3+	9 415 (23.6)
				SLI+TL	29 679 (74.5)		
Endovascular and open	4 558	3 231 (70.9)	70 (64 to 77)	**IC**	966 (21.20	**0**	4 97 (10.9)
				SLI	2 605 (57.2)	**1**	2 392 (52.5)
				TL	987 (21.7)	**2**	421 (9.2)
						3+	1 248 (27.4)
				SLI+TL	3 592 (78.9)		

[1] IC: intermittent claudication; SLI: severe limb ischaemia without record of tissue loss; TL: severe limb ischaemia with record of tissue loss.
[2] Number of comorbidities: details provided in Online Appendix, Supplementary Table S4.

Table 2. Unadjusted cumulative incidence of major amputation and death after lower limb revascularisation, by procedure and indication

				Cumulative incidence of amputation (%)				Cumulative incidence of death (%)		
Procedure	**Indication** [1]	**N (%)**	**Amputation**	**Years of follow-up**			**Death**	**Years of follow-up**		
			N (%)	1	3	5	N (%)	1	3	5
Endovascular	IC	26 579	1 051 (4.0)	2.8	3.7	4.2	5 641 921.2)	7.6	16.5	24.7
	SLI	67 416	3 067 (4.6)	4.6	6.0	6.9	14 066 (20.9)	10.0	21.4	31.5
	TL	26 468	4 004 (15.1)	12.6	16.5	18.7	11 012 (41.6)	20.1	39.9	55.2
	SLI+TL	93 884	7 071 (7.5)	5.6	7.4	8.4	25 078 (26.7)	11.2	23.2	33.7
	All	120 463	8 122 (6.7)	4.2	5.6	6.4	30 719 (25.5)	9.8	20.8	30.7
Open	IC	10 145	1 013 (10.0)	7.1	9.4	10.6	2 615 (25.8)	10.8	20.4	29.2
	SLI	21 580	2 196 (10.2)	9.0	12.0	13.5	5 189 (24.1)	12.2	22.8	32.4
	TL	8 099	1 835 (22.7)	17.6	22.9	25.6	2 958 (36.5)	17.8	32.3	44.6
	SLI+TL	29 679	4 031(13.6)	10.1	13.4	15.0	8 147 (27.5)	12.8	23.8	33.7
	All	39 824	5 044 (12.7)	8.8	11.6	13.1	10 762 (27.0)	12.1	22.6	32.2
Endovascular and open	IC	966	72 (7.5)	5.3	7.2	8.3	244 (25.3)	10.8	21.6	31.9
	SLI	2 605	176 (6.8)	6.7	9.2	10.4	528 (20.3)	11.1	22.2	32.7
	TL	987	206 (20.9)	16.3	21.9	24.7	317 (32.1)	16.3	31.5	45.0
	SLI+TL	3 592	382 (10.6)	8.3	11.3	12.8	845 (23.5)	12.0	23.6	34.6
	All	4 558	454 (10.0)	6.8	9.2	10.5	1 089 (23.9)	11.5	22.8	33.6

[1] IC: intermittent claudication; SLI: severe limb ischaemia without record of tissue loss; TL: severe limb ischaemia with record of tissue loss.

Table 3. Unadjusted cumulative incidence of composite outcome and amputation-free survival, by procedure and indication

Procedure	Indication[1]	N procedures	Amputation N (%)	Cumulative incidence of composite outcome (%) [2, 3] 1 year	3 years	5 years	Amputation-free survival (%) [2,3] 1 year	3 years	5 years
Endovascular	IC	26 579	1 051 (4.0)	10.4	20.2	28.9	89.6	79.8	71.1
	SLI	67 416	3 067 (4.6)	14.6	27.4	38.4	85.4	72.6	61.6
	TL	26 468	4 004 (15.1)	32.7	56.4	73.9	67.3	43.6	26.1
	SLI+TL	93 884	7 071 (7.5)	16.8	30.6	42.1	83.2	69.4	57.9
	All	120 463	8 122 (6.7)	14	26.4	37.1	86.0	73.6	62.9
Open	IC	10 145	1 013 (10.0)	17.9	29.8	39.8	82.1	70.2	60.2
	SLI	21 580	2 196 (10.2)	21.2	34.8	45.9	78.8	65.2	54.1
	TL	8 099	1 835 (22.7)	35.4	55.2	70.2	64.6	44.8	29.8
	SLI+TL	29 679	4 031(13.6)	22.9	37.2	48.7	77.1	62.8	51.3
	All	39 824	5 044 (12.7)	20.9	34.2	45.3	79.1	65.8	54.7
Endovascular and open	IC	966	72 (7.5)	16.1	28.8	40.2	83.9	71.2	59.8
	SLI	2 605	176 (6.8)	17.8	31.4	43.1	82.2	68.6	56.9
	TL	987	206 (20.9)	32.6	53.4	69.7	67.4	46.6	30.3
	SLI+TL	3 592	382 (10.6)	20.3	34.9	47.4	79.7	65.1	52.6
	All	4 558	454 (10.0)	18.3	32.0	44.1	81.7	68.0	55.9

[1] IC: intermittent claudication; SLI: severe limb ischaemia without record of tissue loss; TL: severe limb ischaemia with a record of tissue loss.
[2] Amputation or death, whichever occurred first.
[3] Unadjusted estimates.

Table 4. Multivariable-adjusted cumulative incidence of major amputation and death after lower limb revascularisation, by procedure and indication

				Cumulative incidence of amputation (%) [1]				Cumulative incidence of death (%) [1]		
			Amputation	Years of follow-up			Death	Years of follow-up		
Procedure	**Indication**	N (%)	N (%)	1	3	5	N (%)	1	3	5
Endovascular	IC	26 579	1 051 (4.0)	2.8	3.7	4.2	5 641 921.2)	7.0	15.7	24.5
	SLI	67 416	3 067 (4.6)	4.3	5.7	6.5	14 066 (20.9)	8.0	17.9	27.6
	TL	26 468	4 004 (15.1)	12.1	15.9	18.0	11 012 (41.6)	12.3	26.6	39.8
	SLI+TL	93 884	7 071 (7.5)	5.3	7.0	8.0	25 078 (26.7)	8.5	18.8	28.7
	All	120 463	8 122 (6.7)	4.1	5.4	6.1	30 719 (25.5)	8.0	17.8	27.5
Open	IC	10 145	1 013 (10.0)	7.2	9.6	10.8	2 615 (25.8)	9.8	19.1	28.2
	SLI	21 580	2 196 (10.2)	8.8	11.7	13.2	5 189 (24.1)	10.0	19.5	28.7
	TL	8 099	1 835 (22.7)	17.3	22.6	25.3	2 958 (36.5)	12.5	24.2	35.0
	SLI+TL	29 679	4 031(13.6)	10.0	13.2	14.8	8 147 (27.5)	10.3	20.2	29.6
	All	39 824	5 044 (12.7)	8.7	11.6	13.0	10 762 (27.0)	10.1	19.8	29.1
Endovascular and open	IC	966	72 (7.5)	5.2	7.1	8.1	244 (25.3)	10.0	20.5	31.4
	SLI	2 605	176 (6.8)	6.5	8.8	10.1	528 (20.3)	9.5	19.6	30.1
	TL	987	206 (20.9)	16.5	22.2	25.0	317 (32.1)	12.2	24.9	37.4
	SLI+TL	3 592	382 (10.6)	8.1	11.0	12.5	845 (23.5)	10.1	20.7	31.6
	All	4 558	454 (10.0)	6.6	6.0	10.3	1 089 (23.9)	10.1	19.8	29.1

[1] Estimates adjusted for patient age, sex and RCS Charlson score.
IC: intermittent claudication; SLI: severe limb ischaemia without record tissue loss; TL: severe limb ischaemia with a record tissue loss.

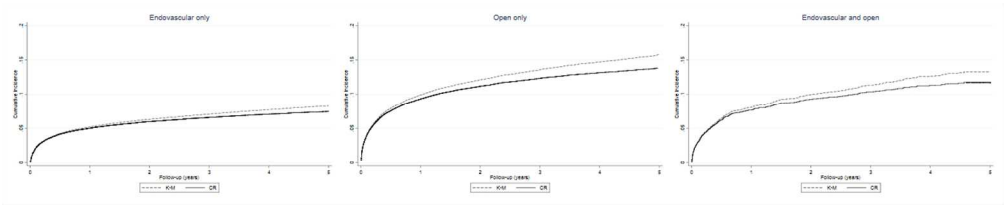

Figure 1. Kaplan-Meier and competing risks estimates of cumulative incidence of amputation following lower limb revascularisation

479x95mm (72 x 72 DPI)

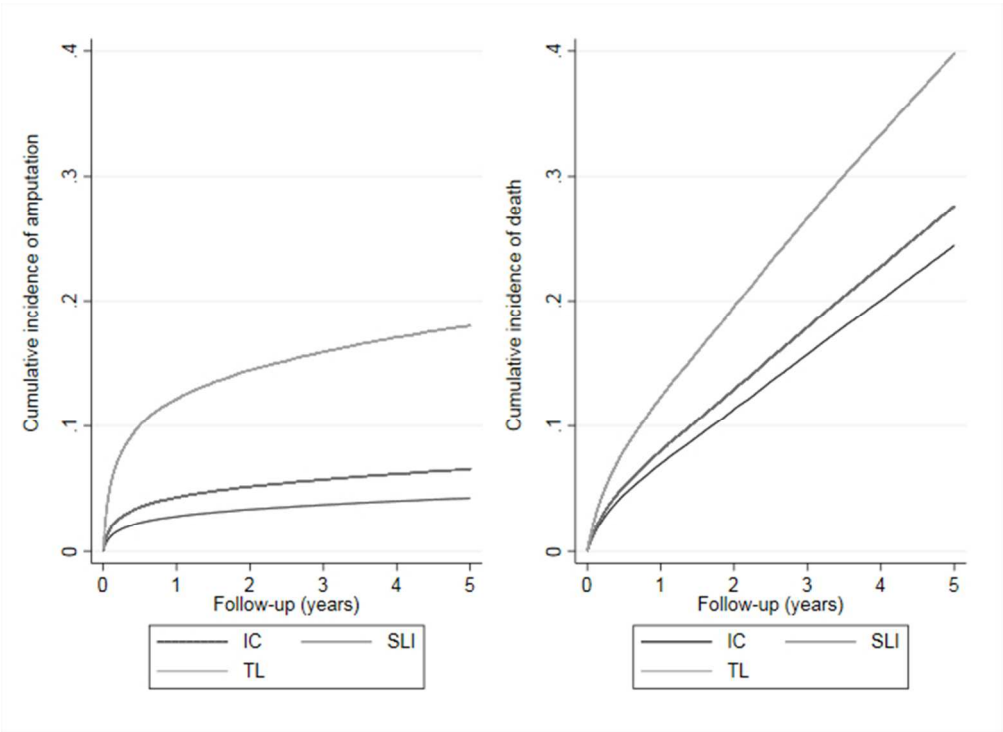

Figure 2. Risk of amputation and death following endovascular revascularisation, by indication

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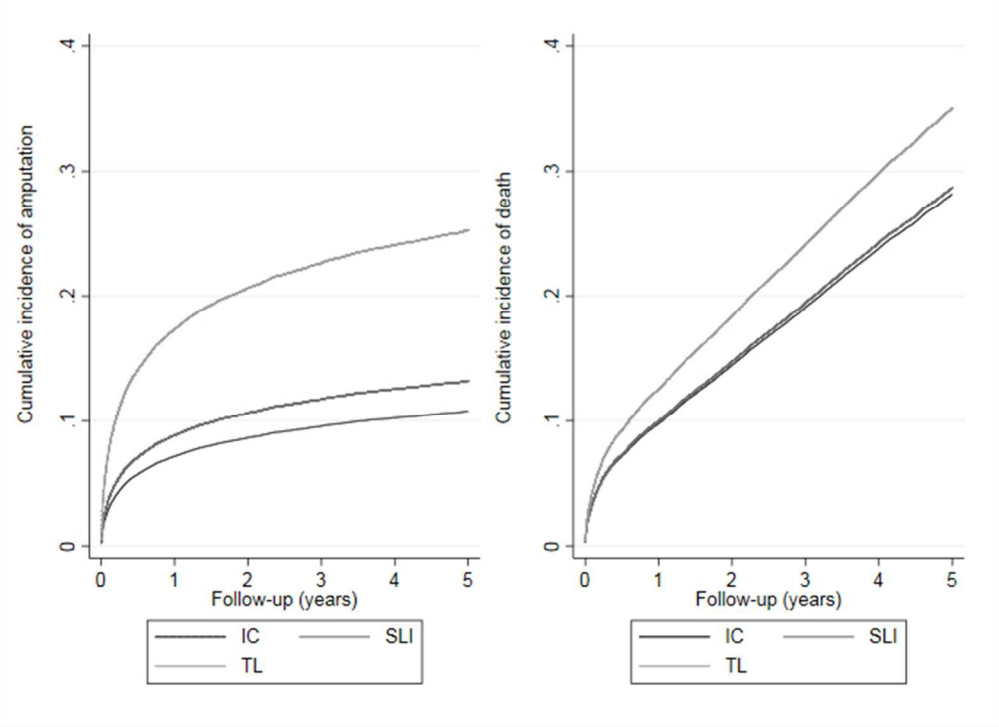


Figure 3. Risk of amputation and death following open revascularisation, by indication

242x176mm (72 x 72 DPI)

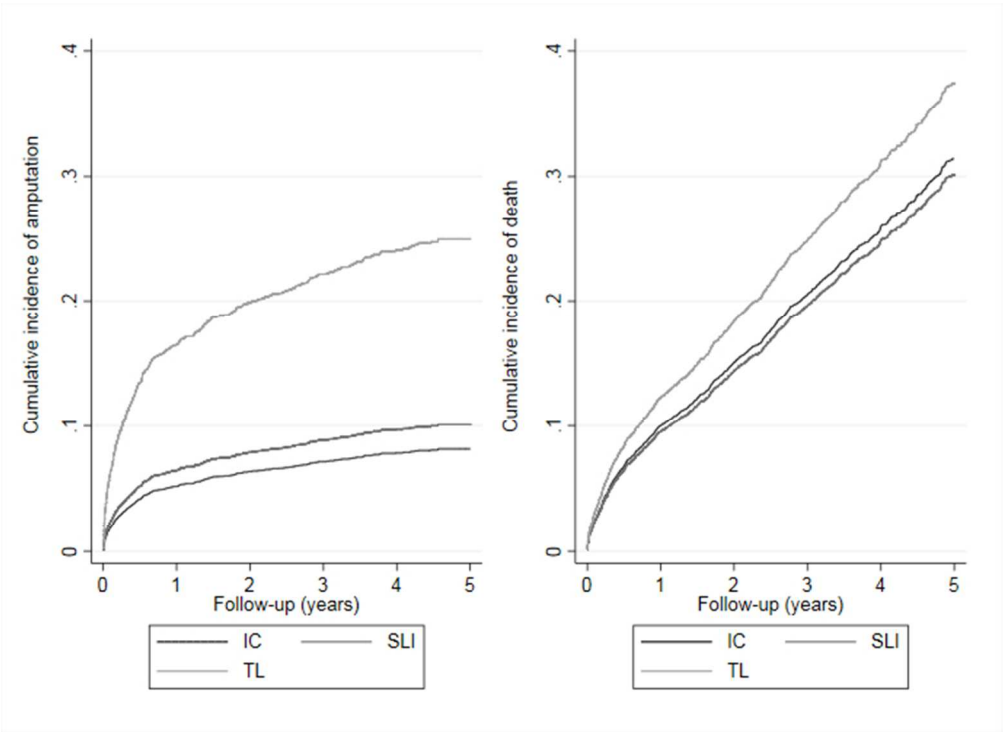


Figure 4. Risk of amputation and death following a combination of endovascular and open revascularisation, by indication

242x176mm (72 x 72 DPI)

Online Appendix. Supplementary Tables and Figures

Supplementary Table S1. Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) version 4.6 codes used to identify open revascularisation

Code	Description
L50.1	Emergency bypass of common iliac artery by anastomosis of aorta to common iliac artery NEC
L50.2	Emergency bypass of iliac artery by anastomosis of aorta to external iliac artery NEC
L50.3	Emergency bypass of artery of leg by anastomosis of aorta to common femoral artery NEC
L50.4	Emergency bypass of artery of leg by anastomosis of aorta to deep femoral artery NEC
L50.5	Emergency bypass of iliac artery by anastomosis of iliac artery to iliac artery NEC
L50.6	Emergency bypass of artery of leg by anastomosis of iliac artery to femoral artery NEC
L50.8	Other specified other emergency bypass of iliac artery
L50.9	Unspecified other emergency bypass of iliac artery
L51.1	Bypass of common iliac artery by anastomosis of aorta to common iliac artery NEC
L51.2	Bypass of iliac artery by anastomosis of aorta to external iliac artery NEC
L51.3	Bypass of artery of leg by anastomosis of aorta to common femoral artery NEC
L51.4	Bypass of artery of leg by anastomosis of aorta to deep femoral artery NEC
L51.5	Bypass of iliac artery by anastomosis of iliac artery to iliac artery NEC
L51.6	Bypass of artery of leg by anastomosis of iliac artery to femoral artery NEC
L51.8	Other specified other bypass of iliac artery
L51.9	Unspecified other bypass of iliac artery
L58.1	Emergency bypass of femoral artery by anastomosis of femoral artery to femoral artery NEC
L58.2	Emergency bypass of femoral artery by anastomosis of femoral artery to popliteal artery using prosthesis NEC
L58.3	Emergency bypass of femoral artery by anastomosis of femoral artery to popliteal artery using vein graft NEC
L58.4	Emergency bypass of femoral artery by anastomosis of femoral artery to tibial artery using prosthesis NEC
L58.5	Emergency bypass of femoral artery by anastomosis of femoral artery to tibial artery using vein graft NEC
L58.6	Emergency bypass of femoral artery by anastomosis of femoral artery to peroneal artery using prosthesis NEC
L58.7	Emergency bypass of femoral artery by anastomosis of femoral artery to peroneal artery using vein graft NEC
L58.8	Other specified other emergency bypass of femoral artery
L58.9	Unspecified other emergency bypass of femoral artery
L59.1	Bypass of femoral artery by anastomosis of femoral artery to femoral artery NEC
L59.2	Bypass of femoral artery by anastomosis of femoral artery to popliteal artery using prosthesis NEC
L59.3	Bypass of femoral artery by anastomosis of femoral artery to popliteal artery using vein graft NEC

Supplementary Table S1, continued.

L59.4	Bypass of femoral artery by anastomosis of femoral artery to tibial artery using prosthesis NEC
L59.5	Bypass of femoral artery by anastomosis of femoral artery to tibial artery using vein graft NEC
L59.6	Bypass of femoral artery by anastomosis of femoral artery to peroneal artery using prosthesis NEC
L59.7	Bypass of femoral artery by anastomosis of femoral artery to peroneal artery using vein graft NEC
L59.8	Other specified other bypass of femoral artery
L59.9	Unspecified other bypass of femoral artery
L60.1	Endarterectomy of femoral artery and patch repair of femoral artery
L60.2	Endarterectomy of femoral artery NEC
L60.3	Profundaplasty of femoral artery and patch repair of deep femoral artery
L60.4	Profundaplasty of femoral artery NEC
L60.8	Other specified reconstruction of femoral artery
L60.9	Unspecified reconstruction of femoral artery

NEC: not elsewhere classified

Supplementary Table S2. OPCS version 4.6 codes used to identify endovascular revascularisation

Code	Description
L54.1	Percutaneous transluminal angioplasty of iliac artery
L54.4	Percutaneous transluminal insertion of stent into iliac artery
L63.1	Percutaneous transluminal angioplasty of femoral artery
L63.5	Percutaneous transluminal insertion of stent into femoral artery
L66.2	Percutaneous transluminal stent reconstruction of artery
L66.5	Percutaneous transluminal balloon angioplasty of artery
L66.7	Percutaneous transluminal placement of peripheral stent in artery

Supplementary Table S3. ICD-10 codes to identify indications for revascularisation

Disease	ICD-10 codes
Intermittent claudication	I73.9
Severe limb ischaemia	I70.2, I72.4, I73.0-8, I74.3-5, I77.1, I77.9
Diabetes with peripheral circulatory complications	E10.5, E11.5, E14.5
Ulceration	L97.X, L03.0, L98.4
Gangrene	R02.X
Osteomyelitis	M86.6, M86.9

Supplementary Table S4. ICD-10 codes to identify co-morbidities included in the RCS Charlson score (from diagnosis codes in the record of the index admission and previous admissions)

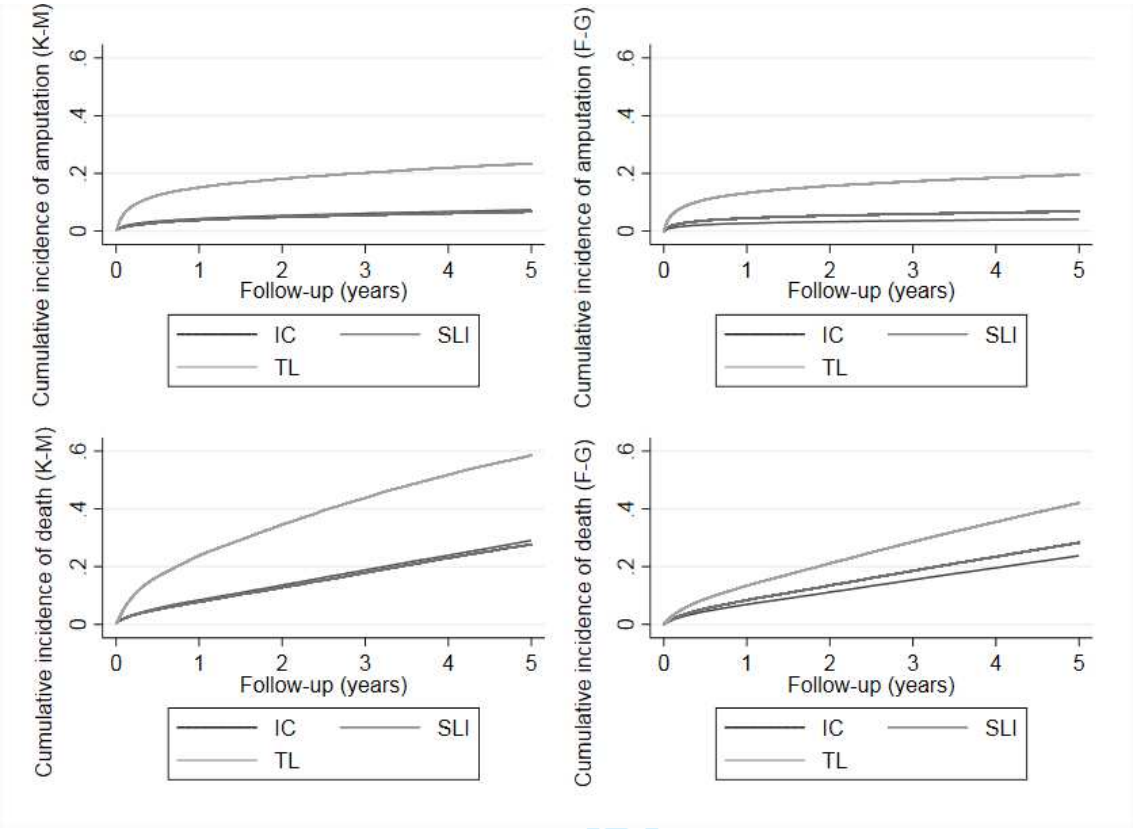
Co-morbidity	ICD-10 codes
Myocardial infarction	I21*, I22*, I23*, I252
Congestive cardiac failure	I11, I13, I255, I42, I43, I50, I517
Cerebrovascular disease	G45, G46, I60–I69
Dementia	A810, F00–F03, F051, G30, G31
Chronic pulmonary disease	I26, I27, J40–J45, J46*, J47, J60–J67, J684, J701, J703
Rheumatological disease	M05, M06, M09, M120, M315, M32–M36
Liver disease	B18, I85, I864, I982, K70, K71, K721, K729, K76, R162, Z944
Hemiplegia or paraplegia	G114, G81–G83
Renal disease	I12, I13, N01, N03, N05, N07, N08, N171*, N172*, N18, N19*, N25, Z49, Z940, Z992
Any malignancy	C00–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C80–C85, C88, C90–C97
Metastatic solid tumour	C77–C79
AIDS/HIV infection	B20–B24

*Acute conditions that were defined as co-morbidities if present in a record of a previous hospital admission within 12 months prior to revascularisation.
AIDS: acquired immune deficiency syndrome; HIV: human immunodeficiency virus.

Supplementary Table S5. OPCS 4.6 codes to identify major lower limb amputations

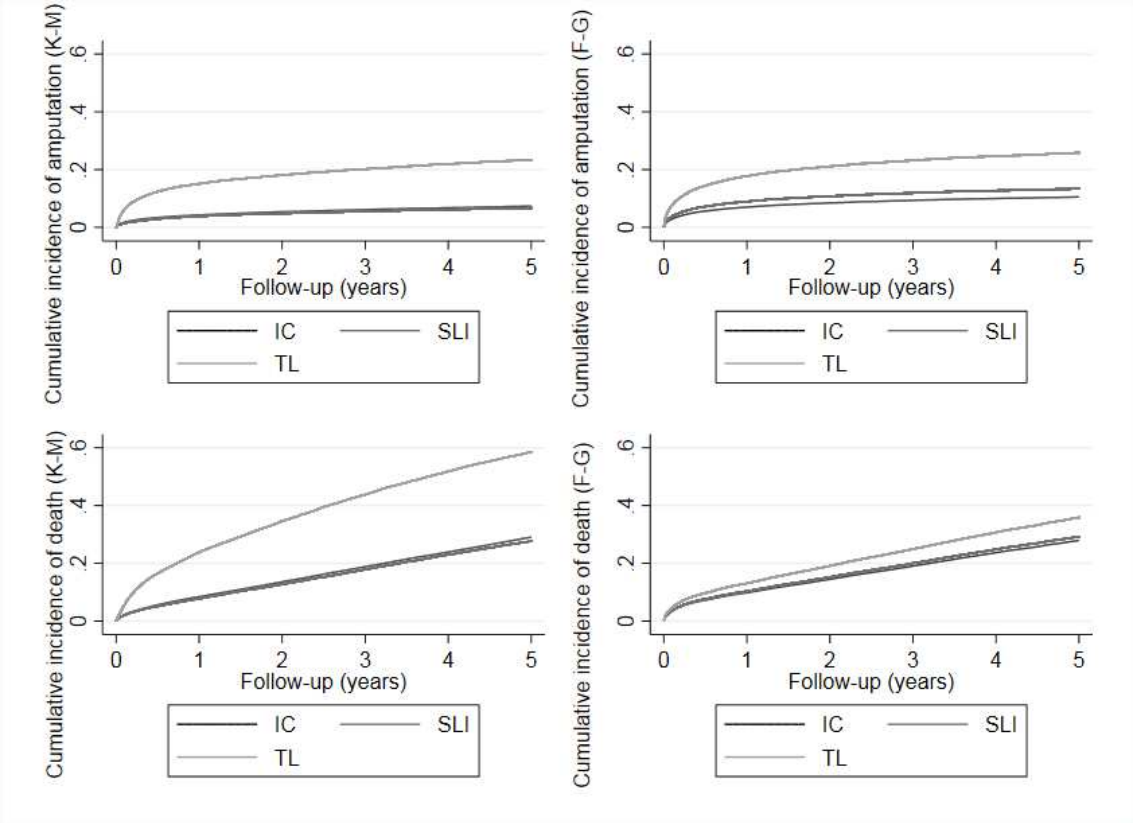
Code	Description
X09.1	Hindquarter amputation
X09.2	Disarticulation of hip
X09.3	Amputation of leg above knee
X09.4	Amputation of leg through knee
X09.5	Amputation of leg below knee
X09.8	Other specified amputation of leg
X09.9	Unspecified amputation of leg

Supplementary Figure S1. Minimum-adjusted[1] risks of amputation and death following endovascular revascularisation, by indication



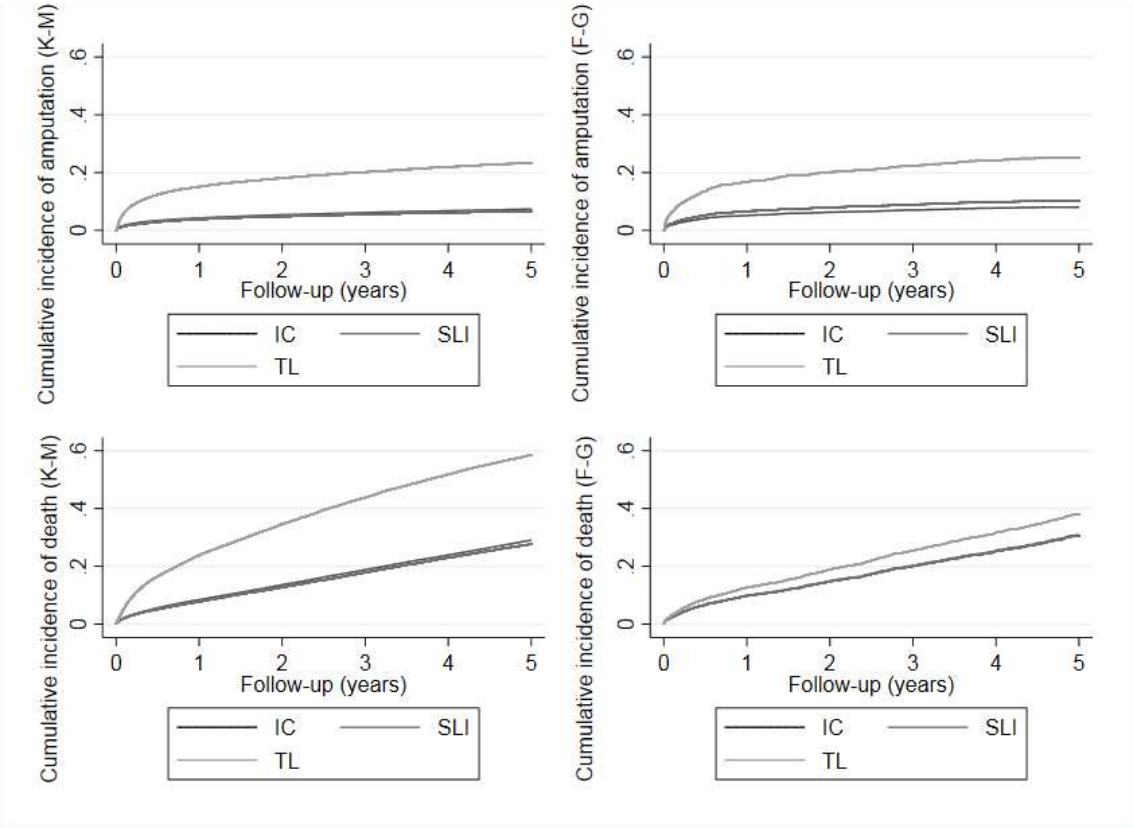
[1] Adjusted for age and sex.
K-M: Kaplan-Meier estimates; F-G: Fine-Gray estimates.
IC: intermittent claudication; SLI: severe limb ischaemia without record tissue loss; TL: severe limb ischaemia with a record tissue loss.

Supplementary Figure S2. Minimum-adjusted[1] risks of amputation and death following open revascularisation, by indication



[1] Adjusted for age and sex.
K-M: Kaplan-Meier estimates; F-G: Fine-Gray estimates.
IC: intermittent claudication; SLI: severe limb ischaemia without record tissue loss; TL: severe limb ischaemia with a record tissue loss.

Supplementary Figure S3. Minimum-adjusted[1] risks of amputation and death following a combination of endovascular and open revascularisation, by indication



[1] Adjusted for age and sex.

K-M: Kaplan-Meier estimates; F-G: Fine-Gray estimates
IC: intermittent claudication; SLI: severe limb ischaemia without record tissue loss; TL: severe limb ischaemia with a record tissue loss.