Illness trajectories after revascularization in patients with peripheral artery disease (PAD): A unified approach to understanding the risk of major amputation and death

Running title:

Illness trajectories following revascularization

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ABSTRACT

Background

The aim of this study was to investigate the illness trajectories of patients with peripheral artery disease (PAD) after revascularization, and estimate the independent risks of major amputation and death (any cause) and their interaction.

Methods

Data from Hospital Episode Statistics Admitted Patient Care (HES APC) were used to identify patients (aged 50+ years) who underwent lower limb revascularization for PAD in England from April 2013 to March 2020. A Markov illness-death model was developed to describe patterns of survival after the initial lower limb revascularization, if and when patients experienced major amputation, and survival after amputation. The model was also used to investigate the association between patient characteristics and these illness trajectories. We also analysed the relative contribution of deaths after amputation to overall mortality and how the risk of mortality after amputation was related to the time from the index revascularization to amputation.

Results

The study analysed 94 690 patients undergoing lower limb revascularization for PAD during 2013-2020. The majority were men (65.6%) and the median age was 72 years (IQR 64-79). A third (34.8%) of patients had non-elective revascularization, whilst others had elective procedures. For non-elective patients, the amputation rate was 15.2% (95% CI 14.4-16.0) and 19.9% (19.0-20.8) at 1 and 5 years after revascularization, respectively. For elective patients, the corresponding amputation rate was 2.7% (95% CI 2.4-3.1) and 5.3% (4.9-5.8). Overall, the risk of major amputation was higher among patients who were younger, had tissue loss, diabetes, greater frailty, non-elective revascularization, and more distal procedures. The mortality rate at 5 years after revascularization was 64.3% (95% CI 63.2-65.5) for non-elective patients and 33.0% (32.0-34.1) for elective patients. After major amputation, patients were at an increased risk of mortality if they underwent major amputation within 6 months after the index revascularization.

Conclusions

The illness-death model provides an integrated framework to understand patient outcomes after lower limb revascularization for PAD. Although mortality increased with age, the study highlights patients under 60 were at higher risk of major amputation, particularly after non-elective revascularization.

Keywords: peripheral artery disease, revascularization, major amputation, mortality, illness trajectories, illness-death model

Non-standard Abbreviations and Acronyms

PAD peripheral artery disease

HES Hospital Episode Statistics

APC Admitted Patient Care

NVR National Vascular Registry

ONS Office for National Statistics

NHS National Health Service

ICD-10 International Classification of Diseases 10th Revision

OPCS-4 Office of Population Censuses and Surveys Classification of Interventions and Procedures 4th Revision

IMD Index of Multiple Deprivation

RCS Royal College of Surgeons

SCARF secondary care administrative records frailty

CLTI chronic limb-threatening ischaemia

Clinical Perspective

What Is New?

- An illness-death model was used to explore the illness trajectories of major amputation and mortality in 94 690 patients who underwent lower limb revascularization for PAD during April 2013 to March 2020 in England.
- Mortality increased with age, but patients under 60 were at a higher risk of major amputation than patients aged 80+ years, particularly after non-elective revascularization.
- Patients had an increased risk of mortality after major amputation if they underwent a major amputation within 6 months of their index revascularization.

What Are the Clinical Implications?

- More than two thirds of major amputations performed in patients following revascularization were after non-elective revascularizations, whilst the majority of major amputations occurred within 6 months of the index revascularization, suggesting precise treatment plans could be developed to help improve patient outcomes.
- Limb salvage following revascularization is particularly poor in patients aged under 60 years, focus is required on timely treatment options that improve the outcomes for this subgroup of patients.
- The overall mortality at 5 years following non-elective revascularization is greater than previously described, suggesting better preventative strategies are warranted.

INTRODUCTION

Peripheral artery disease (PAD) is the third leading cause of atherosclerotic vascular morbidity, after coronary heart disease and stroke[1]. It is an increasingly prevalent condition, and the severe forms of PAD can result in a high risk of lower limb amputation and death[1-3]. Lower limb revascularization is commonly undertaken to improve the blood flow in legs, using either endovascular techniques (angioplasty and/or stenting), open surgery (lower limb bypass procedures, endarterectomy) or a hybrid combination of procedures[2,3]. Two of the primary goals of revascularization are to prevent limb loss and prolong survival[3]. However, a substantial proportion of patients still undergo major lower limb amputation (above the ankle) after revascularization and are at high risk of death[3-8]. The 2022 United Kingdom National Vascular Registry (UK NVR) Annual Report suggested that more than 8% of patients underwent major amputations within 30 days after a non-elective revascularization in 2021[9].

Following an initial lower limb revascularization, patients with PAD may experience major amputation and die afterwards. They may also die without first experiencing a major lower limb amputation. To capture the two important outcomes (major amputation and death), studies evaluating lower limb revascularization procedures often report survival rates and amputation-free survival[5,8]. A limitation of this approach is the lack of information about the risk of major amputation, and how patient characteristics are associated with the individual risks of major amputation and mortality[10]. A competing risk analysis can be used to estimate the separate risks of major amputation and mortality[7,11]. However, this still fails to provide information about the risk of death after amputation and to delineate inferences about overall survival after revascularization. Prognostic studies of survival after major amputation can provide some information, but these studies are often not limited to patients who have had a revascularization[12-15], and therefore interpreting these results and relating them to the disease progression for patients who had previously undergone revascularization is difficult.

The aim of this study was to describe the illness trajectories after revascularization for patients with lower limb PAD, and to investigate the subsequent patterns of major amputation and mortality. Specific objectives were to use a unified approach to examine how patient and clinical characteristics were associated with the risks of: (1) major amputation; (2) death without major amputation; (3) death after major amputation; and (4) overall mortality. The study also investigated whether the risk of death after major amputation was associated with the time from revascularization to amputation, in addition to patient characteristics known at the time of revascularization.

METHODS

Data source and study cohort

This retrospective, population-based cohort study used a dataset extracted from the Hospital Episode Statistics Admitted Patient Care (HES APC) database for England[16], with mortality data taken from the UK Office for National Statistics (ONS) Death Registry which holds the date and cause of death for residents of England and Wales [17]. The HES APC is an administrative database which collects data on all admissions to National Health Service (NHS) hospitals in England, and codes diagnostic information using ICD-10 and operative procedures using OPCS-4. The database allows for longitudinal follow-up of admitted patients using pseudonymized patient identifiers. The data governance arrangements do not allow the authors to redistribute or provide access to the data to other parties. Researchers can apply for access to HES data through NHS Digital (enquiries@nhsdigital.nhs.uk).

Patients who underwent lower limb revascularization with PAD between 1 April 2013 and 31 March 2020 at NHS hospitals in England were identified through the HES APC database (ICD-10 codes for PAD and OPCS-4 codes for lower limb procedures listed in Supplementary Table S1). A patient was classified as having PAD if a relevant ICD-10 diagnostic code occurred in any of the up to 20 diagnosis fields. The first recorded revascularization procedure over the enrolment period was defined as the index revascularization and the procedure date as the index date. The revascularization was labelled elective if performed during an elective admission, and non-elective if performed during an emergency admission or following a transfer from another hospital.

The study cohort consisted of patients who were aged 50 years and over on admission for the index revascularization. We adopted this age cut-off because lower limb revascularization due to PAD is rare among individuals aged under 50 years and the disease may display different patterns of progression[18]. Patients were excluded if they had other lower limb revascularization procedures performed between 1 April 2011 and 31 March 2013 (at least 2 years' look back) so that the index procedure was most likely to be the patients' first revascularization. Patients were also excluded if they had a major amputation on the same day as the index revascularization or prior to the index revascularization from 1 April 2011. The analysis was restricted to patients resident in England at the time of revascularization as non-residents were considered to have a greater risk of loss to follow-up. Patient records with missing data on covariates at the time of index revascularization were also excluded.

Follow-up and outcomes

Follow-up time was defined as the time elapsed from the index date until the date of death, or the end of study date (31 March 2021) for those who survived throughout the study period. This gave a minimum and maximum follow-up period of 1 and 8 years, respectively. The study measured the occurrence of two events during follow-up: major amputation and death. These events were combined to give four primary outcomes (Figure 1): the cumulative incidence of major amputation, the cumulative incidence of death without major amputation, the cumulative incidence of death after major amputation, and the cumulative incidence of overall death.

Patient characteristics at revascularization

Baseline patient and clinical characteristics were taken from the records describing the index revascularization admission. Patient demographics included age, sex and neighborhood socioeconomic deprivation. Deprivation was measured using the English Index of Multiple Deprivation (IMD) related to the patient's area of residence and was converted to quintiles based on the national rank of the area[19]. The PAD indication for revascularization was defined based on whether or not patients presented with tissue loss (ulceration, gangrene, and osteomyelitis) at the time of index revascularization.

Patient comorbidities were captured using the Royal College of Surgeons (RCS) Charlson score[20], which was derived using the diagnostic codes from admission for the index revascularization as well as admissions during the preceding 12 months. Acute conditions (such as myocardial infarction) were only counted when present in the historical admissions. The diagnostic codes for diabetes and PAD were excluded from the formation of RCS Charlson score because diabetes status was examined as a separate variable and PAD formed part of the inclusion criteria. The secondary care administrative records frailty (SCARF) Index[21], which is based on the cumulative deficit model of frailty and comprises 32 deficits that cover medical comorbidities and functional impairment, was used to describe patients' level of frailty (not frail, mild, moderate or severe). Owing to only a small proportion of patients (<6%) categorised as "not frail", those patients were grouped with the "mild" category for the analyses.

The study distinguished between three types of procedure: endovascular (angioplasty/stent), open (bypass/endarterectomy), and hybrid procedures where both endovascular and open surgical operations were performed on the same day. Procedures were defined as bilateral if the lower limb procedures during the admission of index revascularization involved both legs. The arterial location of revascularization procedures was defined as iliac, femoral, popliteal or crural.

Statistical analysis

Descriptive statistics were used to describe patient and clinical characteristics at the index revascularization. Differences between patient groups were analysed using the Chi-square test. Patients' follow-up times were summarized using the reverse Kaplan-Meier estimator[22,23]. The analyses used a simple, Markov multistate model known as illness-death model[24,25] to describe the disease process and account for the competing risks of amputation and death, and estimate the risks of major amputation and death, with or without major amputation[24]. The model provided an integrated framework to describe the illness trajectories (Figure 1) and to estimate the risks of: (1) major amputation; (2) death without major amputation; (3) death after major amputation; and (4) overall mortality. The model estimates three transition intensities:

(1) transition hazard $h_1(t)$, from revascularization to major amputation;

(2) transition hazard $h_2(t)$, from revascularization to death without major amputation;

(3) transition hazard $h_3(t)$, from major amputation to death.

The relationships between patient characteristics and transition hazards from one state to another were modelled using the flexible parametric proportional hazards model[26-28] (more details on the hazards model can be found in Supplementary Appendix A). The disease trajectories were described using the adjusted cumulative risks of major amputation, death without major amputation, death after having major amputation, and overall death. The trajectories are presented for patients of different ages by admission type recorded at the time of index revascularization. All statistical tests were two-sided and a p-value<0.05 was considered statistically significant. All analyses were done using Stata® MP 17 (StataCorp, College Station, Texas, USA). Results are presented in accordance with the STROBE cohort reporting guidelines[29]. The checklist is provided in the Supplemental

Material. The study involved the secondary analysis of existing pseudonymised data and was therefore exempt from institutional review board approval.

RESULTS

The initial data extract contained records of 98 156 patients with PAD who underwent their first (since 1 April 2011) lower limb revascularization procedures between 1 April 2013 and 31 March 2020. Of these, 3459 (3.5%) were younger than 50 years old at the time of index revascularization and were excluded. Another seven patients were excluded owing to missing data on covariates of age, sex or deprivation index, which left 94 690 patients for analysis.

Baseline patient characteristics

Patient characteristics at the time of index revascularization are summarized in Table 1, stratified by whether the index revascularization was elective or non-elective. The majority were male (65.6%), and the median age was 72 years [interquartile range (IQR) 64-79]. Overall, 39.2% of patients had diabetes and more than half (55.5%) of the cohort had at least one Charlson co-morbidity. A third (37.7%) of patients were severely frail. Non-elective patients comprised a third (34.8%) of the study cohort. Compared with those undergoing elective procedures, patients who had non-elective revascularizations tended to be older (% ≥80 years: 33.0% vs 20.1%, p<0.001), were more likely to have diabetes (51.8% vs 32.5%, p<0.001) and tissue loss (60.5% vs 18.7%, p<0.001), and were likely to be frailer (% moderate/severe: 89.4% vs 61.9%, p<0.001). The proportions of patients with non-elective and elective revascularization procedures that involved popliteal or crural arteries were 40.0% and 19.8%, respectively (p<0.001).

Outcome events after revascularization

The median follow-up time was 4.9 years (IQR 3.0-6.5). At the end of follow-up, 51 658 (54.6%) patients were alive without a major amputation, 4119 (4.3%) were alive with major amputation, 5345 (5.6%) were dead after major amputation, and 33 568 (35.5%) were dead without a major amputation (Figure 1). In total, 9464 (10.0%) patients underwent major amputation during the follow-up interval. Of these, two thirds (66.8%) were non-elective patients at the index admission and more than half (56.5%) had died by the end of study. Supplementary Table S2 summarises how patients moved through different states at specific times after revascularization.

Relationship between patient factors and transition hazards between states

The regression coefficients of patient factors for each transition process are presented in Figure 2 and Supplementary Table S3. The side of procedure was not associated with any transition hazard and was not included in the regression models. The figure highlights a greater transition hazard associated with non-elective revascularizations compared to elective revascularizations with respect to major amputation after revascularization (transition 1), and death without major amputation (transition 2), after adjusting for other covariates. However, the type of index admission for revascularization was no longer associated with the hazard of death from amputation (transition 3). Whether a patient had tissue loss at the time of their index revascularization exhibited a similar pattern, and was only associated with the transition hazards of major amputation after revascularization and death without major amputation. Diabetes was statistically significantly associated with an increased hazard in all three transition processes. The location of the revascularization was most strongly associated with the hazard of amputation after revascularization (transition 1).

There was a negative association between increasing age and the transition hazard from revascularization to amputation, with younger patients having a higher hazard than those aged 80 years and over. Nonetheless, older age was strongly associated with a higher hazard of death after both revascularization (transition 2) and major amputation (transition 3). Frailty was more strongly associated with the hazard of amputation after revascularization than the RCS Charlson comorbidity score, whereas both factors were associated with a higher hazard of death without amputation (transition 2). The RCS Charlson comorbidity calculated at the time of index revascularization was more strongly associated with death after major amputation (transition 3) than frailty.

Competing risks of major amputation and death

Figure 3 presents the trajectories for specific patient subgroups and illustrates how the relationships described in the previous section convert into the cumulative probabilities of major amputation and death without amputation after the index revascularization. Trajectories are shown for elective and non-elective revascularization for patients of different age bands. The other patient characteristics were fixed and describe a man with diabetes who was moderately frail but had no other co-morbidities, and had tissue loss when undergoing endovascular revascularization.

Figure 3 highlights the high risk of major amputation in years after revascularization for non-elective admissions among patients aged between 50 and 54, being 18.0% (95% CI 16.0-20.0) and 28.8% (95% CI 26.0-31.7) at 1 and 5 years, respectively (Supplementary Table S4). This risk decreased among older patients, being 11.9% (95% CI 10.6-13.2) and 17.0% (95% CI 15.4-18.7) for patients aged between 80 and 84 at 1 and 5 years. Among patients who underwent an elective revascularization, the risk of major amputation remained comparatively low whatever the patients' age. Specifically, the cumulative risk of major amputation at 5 years after revascularization was 10.8% (95% CI 9.4-12.2) for patients aged 50-54 years, and 6.5% (95% CI 5.7-7.4) for those aged 80-84 years. However, the risk of death without a major amputation increased substantially among older patients after both elective and non-elective revascularizations.

Supplementary Figures S1(a) - (e) illustrate how other patient factors influence the cumulative probabilities of major amputation and death without major amputation after revascularization for elective and non-elective patients.

Risk of death after major amputation

The illness-death model enabled the association between the risk of death after major amputation and the time from revascularization to major amputation to be explored, in addition to the impact of patient characteristics. The estimated relationship is illustrated in Figure 4 and Supplementary Figure S2. Specifically, Figure 4 shows how the 1-year mortality rate after major amputation changes with the time from revascularization to major amputation across different age groups. Patients who underwent major amputation within a year of revascularization had a significantly increased 1-year mortality rate, particularly for those who underwent major amputation within the first 6 months. For patients aged 80-84 years at revascularization, the adjusted 1-year mortality rates after major amputation were 39.2% (95% CI 35.1-43.2) and 29.8% (95% CI 26.5-33.1) for those who underwent major amputation at 3 months and 1 year after revascularization, respectively. For patients aged 50-54 years, the corresponding 1-year mortality rates were 20.3% (95% CI 17.3-23.2) and 14.9% (95% CI 12.6-17.2), respectively. The cumulative probabilities of death after major amputation in relation to some specific times to major amputation is presented in Supplementary Figure S2 for a selection of patient subgroups.

Cumulative incidence of overall mortality

The adjusted risks of overall mortality after elective and non-elective revascularization for patients of different ages are summarised in Figure 5. It also shows the relative contributions of death after amputation and death without amputation. For both elective and non-elective revascularizations, deaths following amputation contribute a small proportion to overall mortality. Its relative contribution was largest in patients aged 50-54 years who had a non-elective revascularization. For this age-group, the adjusted overall mortality rate at 5 years after the index revascularization was 27.4% (95% CI 25.0-29.8), of which 38.7% was contributed from the mortality after having a major amputation. In contrast, the adjusted overall 5-year mortality rate was 69.9% (95% CI 67.9-71.9) for those aged 80-84 years, of which 15.7% was contributed by mortality after amputation.

Mortality after major amputation contributed only marginally to the overall mortality for patients who had elective revascularization. This was because these patients had a lower risk of major amputation. Nonetheless, the risks of death after amputation were similar between patients who had non-elective and elective revascularizations. Supplementary Figure S3 depicts the comprehensive trajectories of state occupation probabilities after revascularization. Supplementary Figures S4 (a) – (e) illustrate how other patient factors influenced the adjusted overall mortality after the index revascularization for elective and non-elective patients.

DISCUSSION

Improving outcomes for patients with PAD requires a better understanding of how the disease progresses, and how this is associated with patient characteristics. This study used an integrated approach (applied in other diseases [30-33]) to investigate the illness trajectories after revascularization and describe rates of progression to major amputation and death, appropriately accounting for competing risks. Benefits of this approach include being able to estimate how the rate of mortality after major amputation contributed to overall mortality for patients with different characteristics, and explore the relationship between the time from revascularization to amputation and the risk of death after amputation.

Our findings highlight various factors related to illness trajectories. An important theme was the poor prognosis of patients with PAD admitted non-electively for revascularization. The majority of patients who have a non-elective revascularization are believed to be admitted with chronic limb-threatening ischaemia (CLTI)[34,35]. Various studies have highlighted the poor outcomes experienced by these patients[3-5]. For example, a population-based study in the UK by Howard et al.[36] reported an amputation-free survival rate at 5 years of 27.1% for patients with CLTI. Although this study could not explicitly label patients with CLTI (due to the limitations of ICD-10 diagnostic codes used in HES[37]), we note the estimated rate of amputation-free survival at 5 years was similar and at 28.3% for non-elective patients (Supplementary Table S2). Indeed, at 5 years after the index revascularization the overall mortality rate was 64.3%, where 51.8% was contributed to by the mortality without major amputation and 12.5% was by the mortality after major amputation. A Dutch national registry study[38] reported an all-cause mortality rate of 57% at 5 years in patients with CLTI. Birmpili et al.[39] estimated a mortality of 49.4% (without major amputation) at 5 years after minor amputation. A greater mortality rate was reported for patients who underwent non-elective revascularization. It could suggest room to improve patient selection for revascularization and some patients might be better managed with primary amputation or conservative treatment[40].

The study highlights how the association between the illness trajectories and patient characteristics is not straightforward, as illustrated by the estimated transition hazards. While older patient age at revascularization was associated with a marked increased risk of all-cause mortality, the risk of major amputation after revascularization was lower for older patients than younger patients. Such findings were also reported by Kim et al.[18,41]. Using HES data, McCaslin et al.[42] noted a marked decline of amputations in England among patients aged over 75 years from the mid-1990s. Birmpili et al.[39] also suggested an increased risk of major amputation among younger patients than older patients after undergoing a minor amputation with diabetics and/or PAD. However, some studies found the opposite relationship[6,43]. The reasons for this are unclear but it might reflect the use of the standard Kaplan-Meier approach which fails to account for the competing risk of death. Older patients had a high risk of all-cause mortality after revascularization, and this could distort the estimated association between age and the risk of major amputation. Our study has appropriately accounted for the competing risk of death when evaluating patients' risk of major amputation. The results may also reflect that a greater proportion of younger patients have insulin-dependent diabetes, are current smokers or may have renal impairment, factors which are associated with accelerated atherosclerosis leading to early presentations of severe forms of PAD and progression to limb loss[18,41]. Additionally, older patients with PAD could be more likely to be managed conservatively than younger patients, owing to a higher risk of all-cause mortality and the likelihood of being too frail to undergo a major amputation after revascularization.

As with other studies[44,45], the current study demonstrated a strong association between neighborhood deprivation and the rate of major amputation, whereas its association with mortality was more moderate. Further work is warranted to explore whether this association reflects an inequality of access to vascular services in patients with PAD, and whether reducing the rate of major amputation in the most deprived areas could subsequently improve overall survival. A diagnosis of diabetes was associated with increased risks of major amputation and death after revascularization. However, after adjusting for other patient characteristics, its effect was moderate compared with the effect sizes for patient comorbidities and frailty. Patients' comorbidities were strongly associated with both death without amputation and death after amputation, but had only a small effect on the risk of major amputation after revascularization. In contrast, patient frailty was strongly associated with each transition hazard between the health states.

A feature of this study was an exploration of the relationship between the time to major amputation and the risk of mortality thereafter. Patients had a significantly increased risk of mortality in the next few years if they underwent a major amputation within six months after the index revascularization, compared to those who had a major amputation after six months. Further research is required to explore whether these patients could be better served with a primary amputation or non-operative management in the first place[40].

The main strength of this study is the novel use of the illness-death model to make inferences for the illness trajectories of major amputation and death after revascularization in patients with PAD. This approach appropriately accounted for competing risks for making inferences on both major amputation and death after revascularization. Inferences on mortality after amputation were provided as well. Additionally, recent nation-wide, long-term follow-up data were used in this study to provide real world evidence with current revascularization techniques on the outcomes of patients with PAD.

The study has several potential limitations. Firstly, repeated revascularizations after the index procedure might indicate a worse disease trajectory in patients with PAD. However, for simplicity, it did not form part of the multistate model. Secondly, the limitations of ICD-10 diagnostic codes used in HES meant that the severity of PAD was not classified using a standard scale such as the Fontaine score. Severity of disease was categorised simply based on presentation with / without tissue loss, and whether or not a patient had a non-elective or elective revascularization. Also, the ICD-10 diagnostic codes used in HES could not properly identify revascularizations because of acute limb ischaemia[37]. Such patients could constitute a small proportion of the study cohort. Thirdly, the laterality of disease was not taken into account, therefore a subsequent major amputation may have occurred on either limb. Fourthly, the study indicated that the location of PAD might be associated with an increased risk of major amputation. However, the HES APC database only captures the location of revascularization procedures which gives an approximate location of PAD. Finally, there is a risk of residual confounding due to unmeasured confounding variables, for example, patients' medication usage and smoking status, which are not available in HES. Ethnicity was not accounted for in this study due to the uncertain reliability of ethnicity data collected in HES. These may partly explain why the admission mode for revascularization remained a strongly significant factor after adjusting for patient and clinical characteristics.

CONCLUSIONS

The illness-death model provides an integrated framework to understand patient outcomes after lower limb revascularization for PAD, appropriately accounting for competing risks, and highlights the range of trajectories experienced by different patient subgroups. Although mortality increases with age, the risk of major amputation decreases. Younger patients aged 60 under had a significantly increased risk of major amputation after non-elective revascularizations. More than two thirds of major amputations performed in patients who previously had revascularization were after non-elective revascularizations, and mainly occurred within 6 months after the index revascularization. The cumulative incidence of major amputation was generally high at 5 years among those with severe forms of PAD and undergoing non-elective revascularization. However, more than half of these patients could have died within 5 years after the major amputation. The relative contribution of death with major amputation to overall mortality varied with the age at index revascularization, owing to the varying risks of major amputation for patients at different age bands. This study provides important evidence with clinical and policy implications. Precise treatment plans could be developed based on the findings of this study to help improve patient outcomes.

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Disclosures

None.

Supplemental Materials

Appendix A: Flexible parametric proportional hazards model

Table S1

Table S2

Table S3

Table S4

Figure S1(a)-(e)

Figure S2

Figure S3

Figure S4(a)-(e)

STROBE cohort checklist

REFERENCES

1. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. The lancet. 2013; 382:1329-1340.
2. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, Mills JL, Ricco JB, Suresh KR, Murad MH, Aboyans V. Global vascular guidelines on the management of chronic limb-threatening ischemia. European Journal of Vascular and Endovascular Surgery. 2019; 58:S1-109.
3. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-society consensus for the management of peripheral arterial disease (TASC II). Journal of vascular surgery. 2007; 45:S5-S67.
4. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, Ruckley CV, Raab GM, trial Participants BA. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: an intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. Journal of vascular surgery. 2010; 51:5S-17S.
5. Bradbury AW, Ruckley CV, Fowkes FG, Forbes JF, Gillespie I, Adam DJ. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet. 2005; 366:1925-1934.
6. Fridh EB, Andersson M, Thuresson M, Sigvant B, Kragsterman B, Johansson S, Hasvold P, Falkenberg M, Nordanstig J. Amputation rates, mortality, and pre-operative comorbidities in patients revascularised for intermittent claudication or critical limb ischaemia: a population based study. European Journal of Vascular and Endovascular Surgery. 2017; 54:480-486.

7. Heikkila K, Loftus IM, Mitchell DC, Johal AS, Waton S, Cromwell DA. Population-based study of mortality and major amputation following lower limb revascularization. Journal of British Surgery. 2018; 105:1145-1154.
8. Gray WK, Day J, Horrocks M. Outcomes for angioplasty and bypass lower limb revascularisation procedures for limb salvage in England: findings from the Getting it Right First Time programme. European Journal of Vascular and Endovascular Surgery. 2020; 60:711-719.
9. Waton S, Johal A, Birmpili P, Li Q, Atkins E, Cromwell DA, Williams R, Pherwani AD. National Vascular Registry: 2022 Supplementary Report. London: The Royal College of Surgeons of England. 2022.
10. Moxey PW, Hofman D, Hinchliffe RJ, Jones K, Thompson MM, Holt PJ. Trends and outcomes after surgical lower limb revascularization in England. Journal of British Surgery. 2011; 98:1373-1382.
11. Heikkila K, Mitchell DC, Loftus IM, Johal AS, Waton S, Cromwell DA. Improving 1-year outcomes of infrainguinal limb revascularization: population-based cohort study of 104 000 patients in England. Circulation. 2018; 137:1921-1933.
12. Aulivola B, Hile CN, Hamdan AD, Sheahan MG, Veraldi JR, Skillman JJ, Campbell DR, Scovell SD, LoGerfo FW, Pomposelli Jr FB. Major lower extremity amputation: outcome of a modern series. Archives of surgery. 2004; 139:395-399.
13. Taylor SM, Kalbaugh CA, Blackhurst DW, Hamontree SE, Cull DL, Messich HS, Robertson RT, Langan III EM, York JW, Carsten III CG, Snyder BA. Preoperative clinical factors predict postoperative functional outcomes after major lower limb amputation: an analysis of 553 consecutive patients. Journal of vascular surgery. 2005; 42:227-234.
14. Moxey PW, Hofman D, Hinchliffe RJ, Poloniecki J, Loftus IM, Thompson MM, Holt PJ. Delay influences outcome after lower limb major amputation. European Journal of Vascular and Endovascular Surgery. 2012; 44:485-490.

15. Jones WS, Patel MR, Dai D, Vemulapalli S, Subherwal S, Stafford J, Peterson ED. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. American heart journal. 2013; 165:809-815.
16. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data resource profile: hospital episode statistics admitted patient care (HES APC). International journal of epidemiology. 2017; 46:1093-1093i.
17. Deaths - Office for National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths (accessed 26 September 2022)
18. Kim TI, Aboian E, Fischer U, Zhang Y, Guzman RJ, Chaar CI. Lower extremity revascularization for chronic limb-threatening ischemia among patients at the extremes of age. Annals of Vascular Surgery. 2021; 72:517-528.
19. Communities and Local Government. The English indices of deprivation, 2015. Available: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 (accessed 26 September 2022)
20. Armitage JN, Van Der Meulen JH. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. British Journal of Surgery. 2010; 97:772-781.
21. Jauhari Y, Gannon MR, Dodwell D, Horgan K, Clements K, Medina J, Tsang C, Robinson T, Tang SS, Pettengell R, Cromwell DA. Construction of the secondary care administrative records frailty (SCARF) index and validation on older women with operable invasive breast cancer in England and Wales: a cohort study. BMJ open. 2020; 10:e035395.
22. Schemper M, Smith TL. A Note on Quantifying Follow-up in Studies of. Controlled clinical trials. 1996; 17:343-346.
23. Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part I: basic concepts and first analyses. British journal of cancer. 2003; 89:232-238.

24. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Statistics in medicine. 2007; 26:2389-2430.

25. Touraine C, Helmer C, Joly P. Predictions in an illness-death model. Statistical methods in medical research. 2016; 25:1452-1470.

26. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Statistics in medicine. 2002; 21:2175-2197.

27. Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. The Stata Journal. 2009; 9:265-290.

28. Crowther MJ, Lambert PC. Parametric multistate survival models: Flexible modelling allowing transition-specific distributions with application to estimating clinically useful measures of effect differences. Statistics in medicine. 2017; 36:4719-4742.

29. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

30. Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: the importance of multistate models and competing risks analysis. Hepatology. 2015; 62:292-302.

31. Willeumier JJ, Rueten-Budde AJ, Jeys LM, Laitinen M, Pollock R, Aston W, Dijkstra PS, Ferguson PC, Griffin AM, Wunder JS, Fiocco M. Individualised risk assessment for local recurrence and distant metastases in a retrospective transatlantic cohort of 687 patients with high-grade soft tissue sarcomas of the extremities: a multistate model. BMJ open. 2017; 7:e012930.

32. Le-Rademacher JG, Peterson RA, Therneau TM, Sanford BL, Stone RM, Mandrekar SJ. Application of multi-state models in cancer clinical trials. Clinical Trials. 2018; 15:489-498

33. Lyons J, Akbari A, Abrams KR, Lorenzo AA, Dhafari TB, Chess J, Denaxas S, Fry R, Gale CP, Gallacher J, Griffiths LJ. Trajectories in chronic disease accrual and mortality across the

lifespan in Wales, UK (2005–2019), by area deprivation profile: linked electronic health records cohort study on 965,905 individuals. The Lancet Regional Health–Europe. 2023; 32.

34. Waton S, Johal A, Birmpili P, Li Q, Cromwell D, O'Neill R et al. National Vascular Registry. Annual Report. London: Royal College of Surgeons of England. 2021
35. Li Q, Birmpili P, Johal AS, Waton S, Pherwani AD, Boyle JR, Cromwell DA. Delays to revascularization for patients with chronic limb-threatening ischaemia. British Journal of Surgery. 2022; 109:717-726.
36. Howard DP, Banerjee A, Fairhead JF, Hands L, Silver LE, Rothwell PM. Population-based study of incidence, risk factors, outcome, and prognosis of ischemic peripheral arterial events: implications for prevention. Circulation. 2015; 132:1805-1815.
37. Birmpili P, Atkins E, Li Q, Johal AS, Waton S, Williams R, Pherwani AD, Cromwell DA. Evaluation of the ICD-10 system in coding revascularisation procedures in patients with peripheral arterial disease in England: A retrospective cohort study using national administrative and clinical databases. EClinicalMedicine. 2023; 55.
38. Van Haelst ST, Koopman C, Den Ruijter HM, Moll FL, Visseren FL, Vaartjes I, de Borst GJ. Cardiovascular and all-cause mortality in patients with intermittent claudication and critical limb ischaemia. British Journal of Surgery. 2018; 105:252-261.
39. Birmpili P, Li Q, Johal AS, Atkins E, Waton S, Chetter I, Boyle JR, Pherwani AD, Cromwell DA. Outcomes after minor lower limb amputation for peripheral arterial disease and diabetes: population-based cohort study. British Journal of Surgery. 2023:znad134.
40. Nehler MR, Hiatt WR, Taylor Jr LM. Is revascularization and limb salvage always the best treatment for critical limb ischemia?. Journal of vascular surgery. 2003; 37:704-708.
41. Kim TI, Loh S, DeWan A, Murray M, Mojibian H, Mani A, Mena-Hurtado C, Chaar CI. Major adverse limb events among patients with premature peripheral artery disease compared with those at the common age undergoing revascularization in the vascular quality initiative. Annals of Vascular Surgery. 2022; 87:188-197.

42. McCaslin JE, Hafez HM, Stansby G. Lower-limb revascularization and major amputation rates in England. Journal of British Surgery. 2007; 94:835-839.

43. icai Group T. Long-term mortality and its predictors in patients with critical leg ischaemia. European Journal of Vascular and Endovascular Surgery. 1997; 14:91-95.

44. Arya S, Binney Z, Khakharia A, Brewster LP, Goodney P, Patzer R, Hockenberry J, Wilson PW. Race and socioeconomic status independently affect risk of major amputation in peripheral artery disease. Journal of the American Heart Association. 2018; 7:e007425.

45. Heikkilä K, Loftus IM, Waton S, Johal AS, Boyle JR, Cromwell DA. Association of neighbourhood deprivation with risks of major amputation and death following lower limb revascularisation. Atherosclerosis. 2020; 306:11-14.

Table 1. Baseline patient characteristics on admission for the index revascularization

Participants, n (%)	Elective (61 783, 65.2%)	Non-elective (32 907, 34.8%)	Total (94 690)
Male	41 094 (66.5)	21 036 (63.9)	62 130 (65.6)
Age (years)			
50-59	9852 (15.9)	3857 (11.7)	13 709 (14.5)
60-69	18 882 (30.6)	7684 (23.4)	26 566 (28.1)
70-79	20 654 (33.4)	10 510 (31.9)	31 164 (32.9)
80-89	10 852 (17.6)	9033 (27.5)	19 885 (21.0)
90+	1543 (2.5)	1823 (5.5)	3366 (3.6)
Deprivation quintile			
Q1 (least deprived)	10 323 (16.7)	4864 (14.8)	15 187 (16.0)
Q2	11 551 (18.7)	5922 (18.0)	17 473 (18.5)
Q3	12 532 (20.3)	6576 (20.0)	19 108 (20.2)
Q4	12 947 (21.0)	7135 (21.7)	20 082 (21.2)
Q5 (most deprived)	14 430 (23.4)	8410 (25.6)	22 840 (24.1)
Diabetes mellitus	20 099 (32.5)	17 058 (51.8)	37 157 (39.2)
RCS Charlson score (diabetes not included)			
0	31 732 (51.4)	10 422 (31.7)	42 154 (44.5)
1	18 651 (30.2)	10 028 (30.5)	28 679 (30.3)
2	7441 (12.0)	6589 (20.0)	14 030 (14.8)
3+	3959 (6.4)	5868 (17.8)	9827 (10.4)
Scarf frailty index			
Mild	23 572 (38.2)	3474 (10.6)	27 046 (28.6)
Moderate	22 410 (36.3)	9582 (29.1)	31 992 (33.8)
Severe	15 801 (25.6)	19 851 (60.3)	35 652 (37.7)
PAD with record of tissue loss	11 543 (18.7)	19 920 (60.5)	31 463 (33.2)
Procedure localization (most distal)			
Illiac	16 740 (27.1)	3566 (10.8)	20 305 (21.4)
Femoral	32 819 (53.1)	16 190 (49.2)	49 009 (51.8)
Popliteal	7321 (11.8)	6200 (18.8)	13 521 (14.3)
Crural	4903 (7.9)	6952 (21.1)	11 855 (12.5)
Procedure type			
Endovascular	47 170 (76.3)	22 817 (69.3)	69 987 (73.9)
Open	10 992 (17.8)	8055 (24.5)	19 047 (20.1)
Hybrid	3621 (5.9)	2035 (6.2)	5656 (6.0)
Procedure side[ǂ]			
Bilateral	9872 (16.4)	3214 (10.3)	13 086 (14.3)
Right	24 666 (41.1)	13 995 (44.7)	38 661 (42.3)
Left	25 498 (42.5)	14 129 (45.1)	39 627 (43.4)
Financial year			
2013-2014	11 147 (18.0)	5139 (15.6)	16 286 (17.2)
2014-2015	9834 (15.9)	4752 (14.4)	14 586 (15.4)
2015-2016	9205 (14.9)	4719 (14.3)	13 924 (14.7)
2016-2017	8681 (14.1)	4570 (13.9)	13 251 (14.0)
2017-2018	8198 (13.3)	4649 (14.1)	12 847 (13.6)
2018-2019	7801 (12.6)	4556 (13.8)	12 357 (13.0)
2019-2020	6917 (11.2)	4522 (13.7)	11 439 (12.1)

Financial year runs from 1 April to 31 March the following year. RCS, Royal College of Surgeons; PAD, peripheral artery disease. [ǂ]There were 3316 (3.5%) patients with side information missing.

Figure 1: Graphical representation of the illness-death model in relation to the disease progression for peripheral artery disease after the first revascularization procedure. A total of 94 690 patients who had undergone revascularization between 1 April 2013 and31 March 2020 entered the model. A total of four states are included: 1) alive without major amputation, 2) alive with major amputation, 3) dead after major amputation, and 4) dead without major amputation. Patients entered study right after revascularization and were all at state 1 initially. The number within each state box indicates the number of patients in that state at the end of follow-up, followed by percentage over total number of patients. Arrows indicate transitions from one state to another, h(t) next to the arrows indicates the corresponding transition process. The number next to the arrow from state 1 to state 2 indicates the number of patients undergoing major amputation, followed by percentage over the total number of patients.

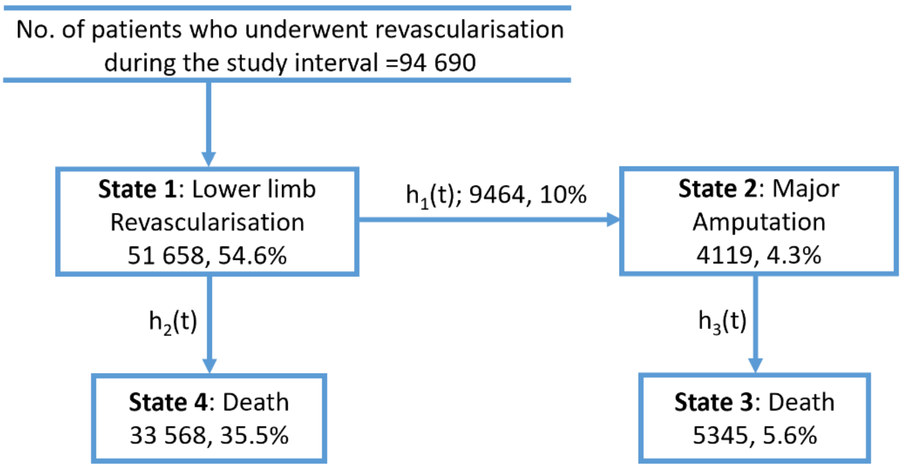

Figure 2. Adjusted hazard ratios for outcomes with respect to three transition processes: Transit 1, from revascularization to major amputation; Transit 2, from revascularization to death (with major amputation); Transit 3, from major amputation to death. The patient factors were covariates included in the multivariable regression models of transition intensities. Revasc, revascularization; Amp, major amputation; RCS, Royal College of Surgeons; PAD, peripheral artery disease.

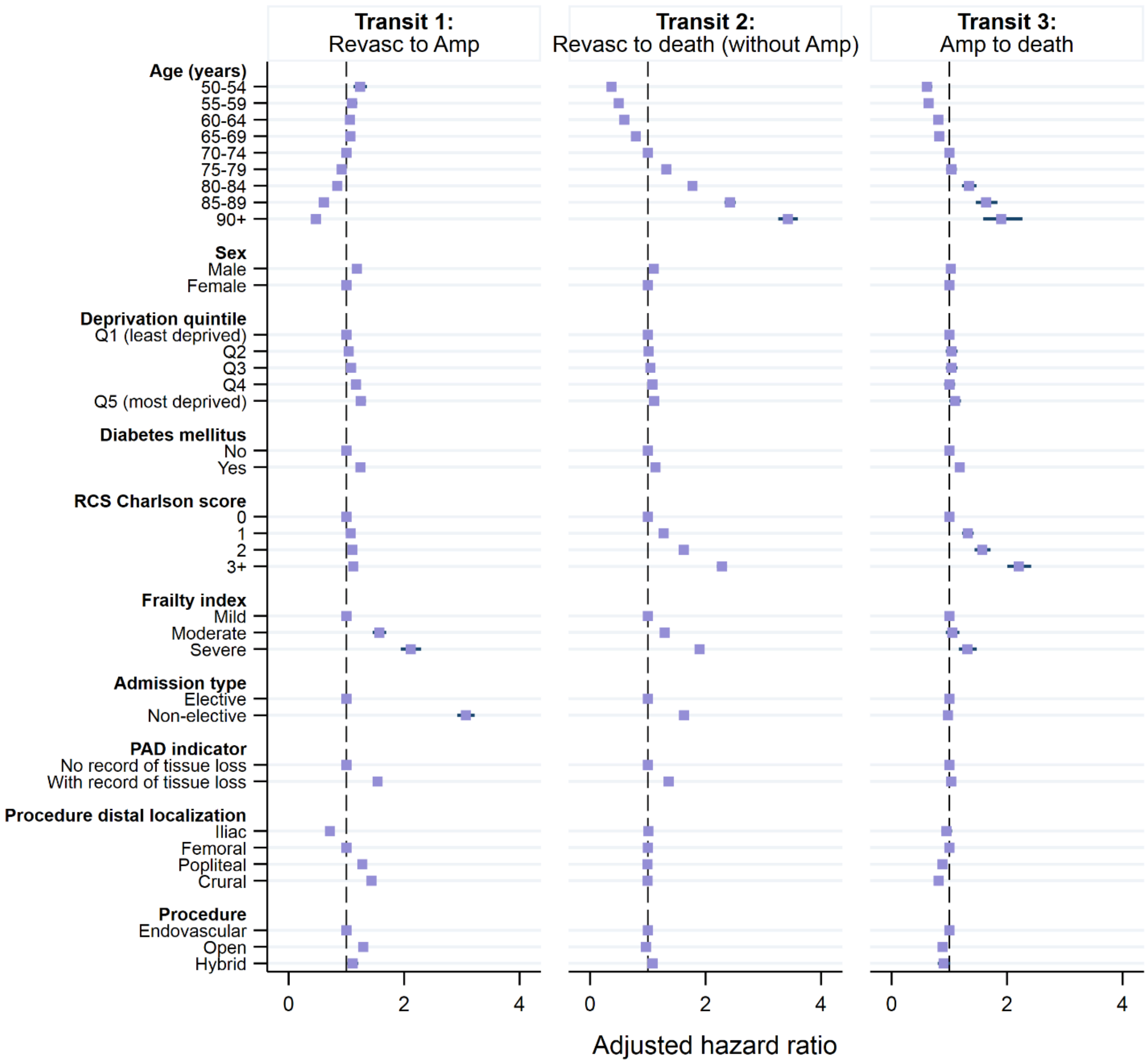

Figure 3. Competing risks of major amputation and mortality (without major amputation) after the index revascularization for elective and non-elective patients. The light grey area represents cumulative incidence of death without major amputation; the dark grey area represents cumulative incidence of major amputation; the white area in the middle represents the probability of a patient remaining alive and without a major amputation. Values of other adjusted covariates are: male, Q3 deprivation index, with diabetes, with a record of tissue loss, RCS Charlson score 0, moderate frailty, femoral procedure distal localization, and endovascular procedure.

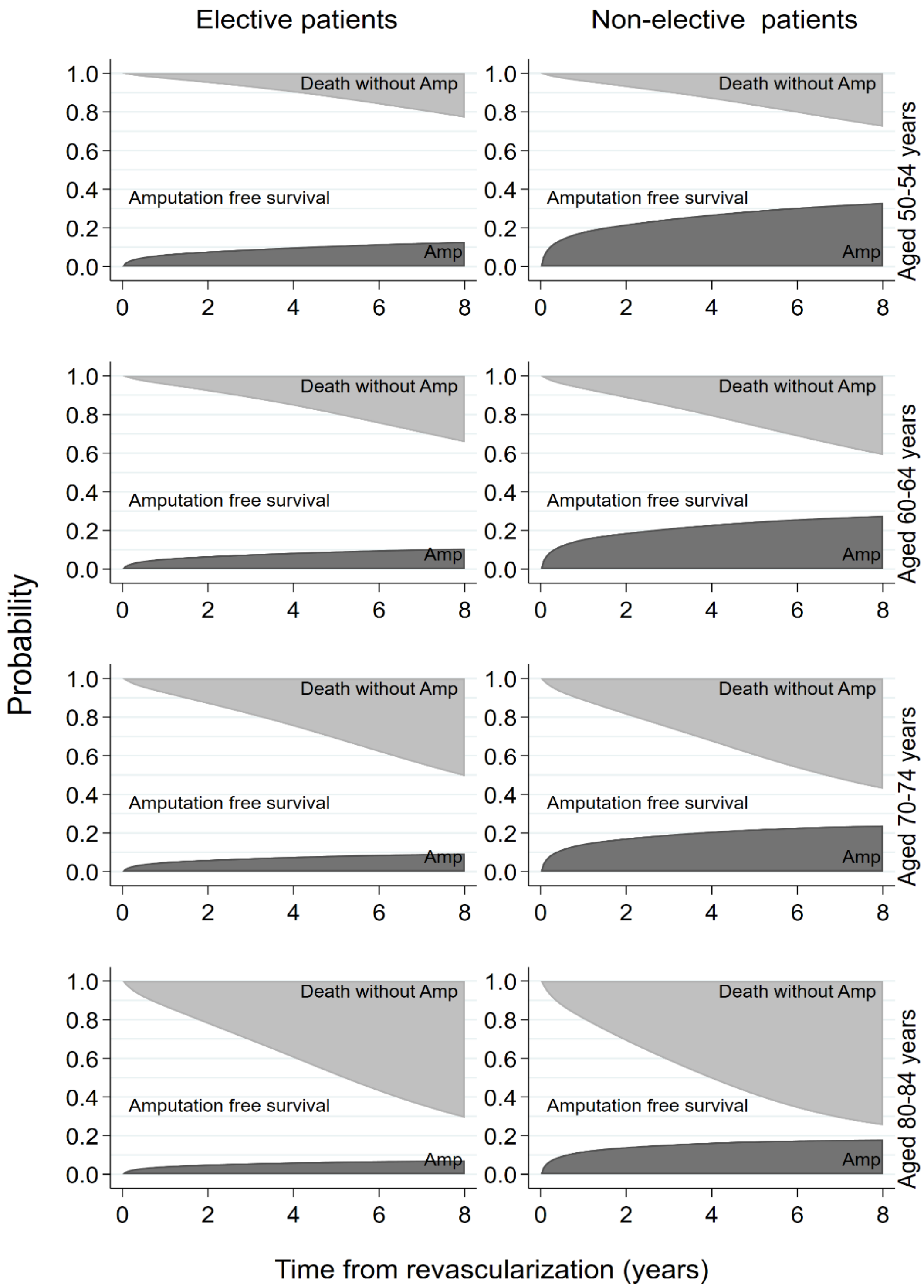

Figure 4. Dynamic risks of mortality at 1 year after major amputation, varying with the time at which patients underwent major amputation after revascularization. Values of other adjusted covariates are: male, Q3 deprivation index, with diabetes, RCS Charlson score 2, moderate frailty, with a records of tissue loss, femoral procedure distal localization, and endovascular procedure.

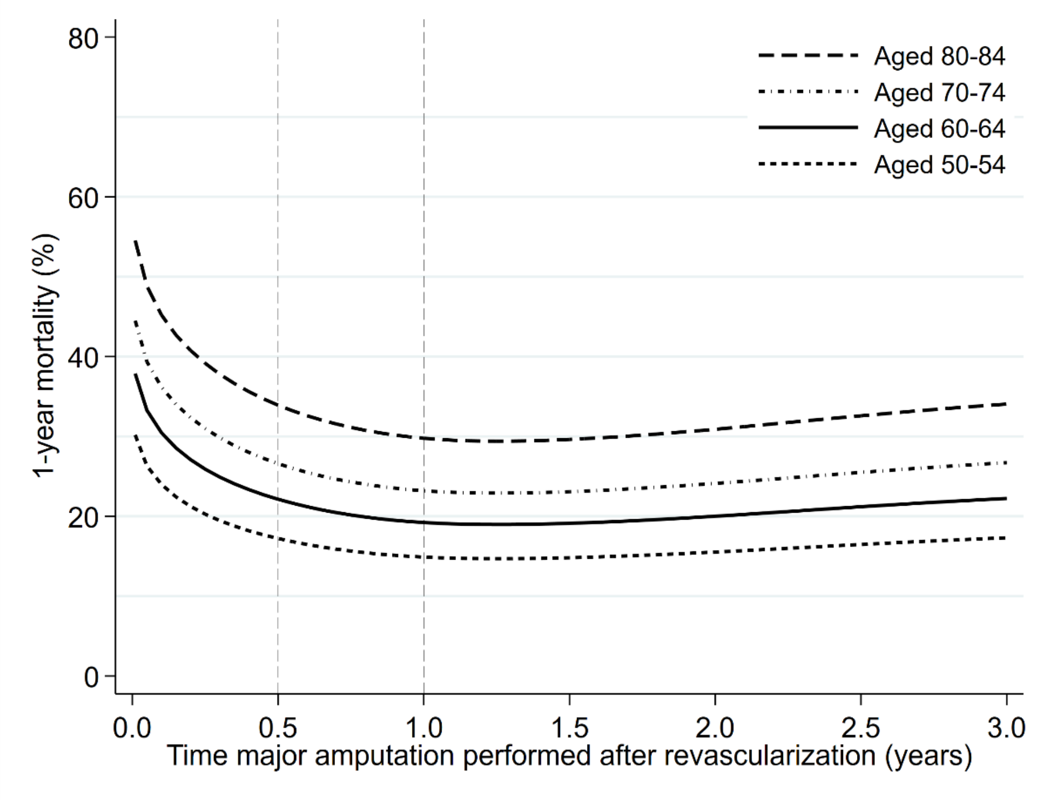

Figure 5. Probability of all-cause death for patients admitted electively and non-electively for the index revascularization. The light grey area represents cumulative probability of death without a major amputation; the dark grey area represents cumulative probability of death with major amputations. Values of other adjusted covariates are: male, Q3 deprivation index, with diabetes, with a record of tissue loss, RCS Charlson score 0, moderate frailty, femoral procedure distal localization, and endovascular procedure.