Clinical Research

Peripheral Artery Disease Leading to Major Amputation: Trends in Revascularization and Mortality Over 18 Years

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Background: Patients with peripheral artery disease (PAD) are at risk for amputation. The aim of this study was to assess the type of revascularization prior to and the 30-day mortality rate after major amputation due to PAD.

Methods: Retrospective analysis of consecutive patients undergoing major amputation for PAD between 01/2000 and 12/2017 at a tertiary referral center. The number and target level of ipsilateral revascularizations prior to amputation were analyzed per patient and over the years. There were 3 types of revascularization (open, endovascular and combined treatment) at 3 levels: aortoiliac, femoropopliteal and infrapopliteal. Univariate and multivariate logistic regression models were used to assess the association of level of amputation and patient characteristics with 30-day mortality.

Results: A total of 312 patients (65.7% male) with a mean age of 73.3 ± 11 years underwent 338 major amputations: 70 (21%) above/through knee and 268 (79%) below knee. A median of 2 (interquartile range, IQR 1–4) revascularizations were performed prior to amputation, with a slight decrease of 1.4% per year from 2000–2017 (incidence rate ratio of 0.986 0.974–0.998; Poisson regression analysis, $P = 0.021$). 16% (53/338) of patients underwent primary amputation without revascularization; this number remained relatively stable throughout the study period. The proportion of exclusively open treatment before amputation decreased substantially from 35% in 2006 to none in 2016, while exclusively endovascular revascularizations were performed increasingly from 17% in 2002 to 64% in 2016. Amputation occurred after a median of 9.5 months (IQR 0.9–67.6 months) if the first revascularization was aortoiliac or femoropopliteal and after 2.1 months (IQR 0.5–13.8 months) if the first intervention was infrapopliteal ($P < 0.001$) with no significant change over the years (normal linear regression, $P= 0.887$). Thirty-day mortality was 8.9% (22/247) after below knee and 27.7% (18/65) after above/through knee amputation (adjusted OR 3.84, 95% CI 1.74–8.54, $P= 0.001$) with a slight increase of mortality over the study period (adjusted OR 1.09, 95% CI 1.018–1.159, Poisson regression analysis, $P= 0.021$). The uni- and multivariate analysis of patient characteristics did not show an association with mortality, except higher ASA classification (adjusted OR 2.65, 95% CI 1.23–5.72, $P= 0.012$).

Conclusions: Mortality, especially after above/through knee amputation, remains high over the past 2 decades. There is a clear shift towards endovascular treatment of patients with PAD prior to major amputation. In patients needing infrapopliteal revascularizations, amputation was performed much sooner than in those with aortoiliac or femoropopliteal interventions, with no improvement over the years. Strategies to extend limb salvage in these patients should be the focus of further research.

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INTRODUCTION

Between 51–93% of all lower limb major amputations are due to peripheral artery disease (PAD),[1] although there is a considerable variation in the incidence of lower limb amputation across the world.[2] Nevertheless, the global prevalence of PAD as well as that of diabetes mellitus, a major contributing factor, is rising. Between 2000–2010 the number of people living with PAD increased by 23.5%[3] and the worldwide prevalence of diabetes has more than doubled.[4]

Major amputation may not only drastically impact a patient's life but is also associated with high mortality rates, ranging from 35–48% within 1 year.[5,6] To extend limb salvage in PAD patients, a better understanding of their treatment before amputation is needed. A recent study from Denmark has shown that only 25% of patients had revascularization within the year prior to amputation.[7] There is an overall trend towards endovascular revascularizations, from 37% in 2002 to 59% in 2014, and a slight decrease in open procedures has been reported.[8] Approximately one third of the patients has more than 1 revascularization before amputation.[8]

Contemporary data on major amputation due to PAD is scarce. The distribution pattern of revascularization procedures prior to amputation has not been well described. Aim of this study was to assess the type and number of revascularizations prior to and the 30-day mortality rate after major amputation due to PAD over an 18-year period at a tertiary referral center.

METHODS

This study was approved by the local ethics committee (2019-00138) and included all patients with PAD due to atherosclerosis who underwent major amputation (defined as below, through or above knee amputation) between January 2000 and December 2017 at the Department of Cardiovascular Surgery at Bern University Hospital, a tertiary referral centre for cardiovascular surgery. Best medical treatment is assigned in all patients, and patients undergo follow-up visits at the outpatient clinic. Patients with acute limb ischemia, popliteal aneurysm and non-atherosclerotic vascular disease leading to amputation were excluded.

The data were retrospectively compiled from patients' medical records. Patient characteristics, cardiovascular risk factors and comorbidities as well as the level of amputation were assessed. Endpoints were the number and type of ipsilateral revascularization procedures prior to amputation, the time from first revascularization to amputation and 30-day mortality thereafter.

Revascularizations were stratified by anatomical location: aortoiliac, femoropopliteal, or infrapopliteal. Treatment modalities included open, endovascular, and combined interventions and were determined by the treating physicians, usually in a multidisciplinary approach. The first intervention at 1 location was recorded by date, every follow-up procedure on the same anatomical region by number. If revascularizations at more than 1 vascular region were performed, every location counted individually. Multiple interventions in the course of 1 hospital stay were registered as individual treatments.

STATISTICAL ANALYSIS

Statistics describing patients' characteristics and descriptive outcomes included median (range) and frequency (percentage). The proportions of interventions by a particular intervention type through time were analyzed using linear regression. Number of revascularizations prior to amputation were analyzed using Poisson regression, incorporating the time between first revascularization and amputation as an offset. Results are presented as incidence rate ratios. Effects of patient characteristics on 30-day mortality were analysed using univariate and multivariate logistic regression and presented as odds ratios (OR). Survival curves were calculated according to the Kaplan-Meier method. Analyses were performed using R version 3.6.3 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

RESULTS

Between 2000 and 2017, 312 patients underwent major amputation due to PAD. Thereof, 26 underwent bilateral amputation, resulting in 338 major amputations being analyzed in this study. The majority of patients were men (65.7 %) and median age was 73.3 years (± 11 standard deviation, SD). Table I shows demographic data and cardiovascular risk profile of all 312 patients.

At amputation, most limbs (304, 90 %) were classified as stage IV and 34 (10 %) had stage III PAD according to Fontaine's classification. The most frequent amputation level was below the knee (268,

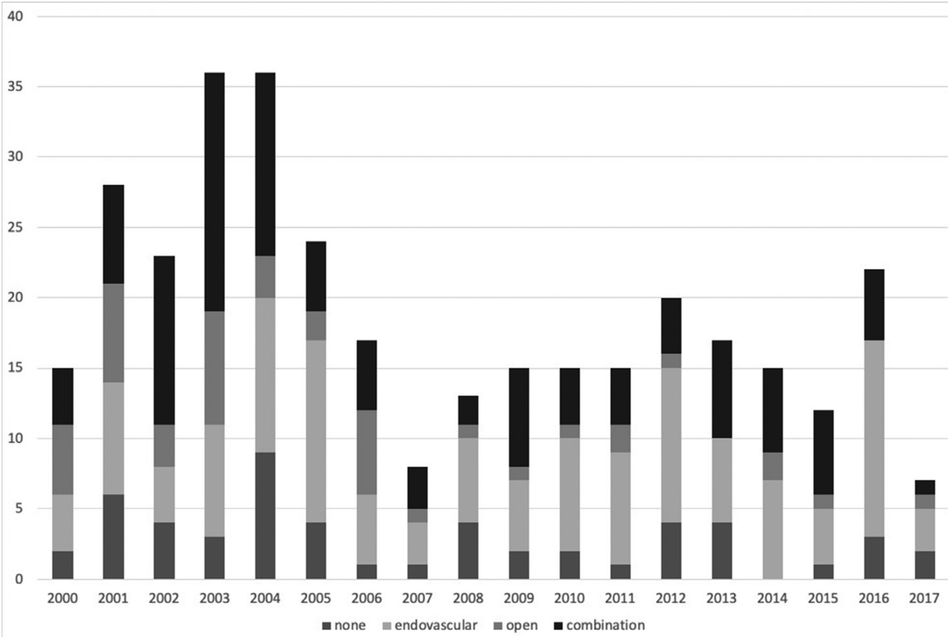

Fig. 1. Number of amputations and distribution of revascularization methods per year between 2000–2017.

Table I. Demographic data and cardiovascular risk profile

	$N = 312$
Age, years	73.3 (11.1)
Male	205 (65.7)
Diabetes	162 (51.9)
Hypertension	236 (75.6)
Dyslipidaemia	134 (42.9)
Smoker	167 (53.5)
Coronary artery disease	164 (52.6)
Renal insufficiency (eGFR < 60ml/min)	161 (51.6)
Steroid medication	23 (7.4)
ASA classification II	7 (2.1)
ASA classification III	217 (69.6)
ASA classification IV	85 (27.2)

Age is mean (±SD), categorical variables are *n* (%).
ASA classification, American Society of Anaesthesiologists physical status classification; eGFR, estimated glomerular filtration rate.

79 %), followed by above the knee (61, 18 %) and through the knee (9, 3 %).

A median of 25 major amputations were performed per year. The highest major amputation rates were recorded in the years 2003 and 2004 with 36 per year and the lowest in 2017 with 7 major amputations. The trends over the years are shown in Fig. 1, reflecting an unsteady yearly number of amputations.

Trends in Revascularization

The trends in revascularization methods are shown in Figs. 1 and 2. A median of 2 (interquartile range, IQR 1–4) revascularizations were performed prior to amputation (Table III). We also found indications that the number of revascularizations prior to amputation decreased through time (incidence rate ratio of 0.986, 95% CI 0.974–0.998; Poisson regression analysis, $P = 0.021$). 16% (53/338) had no revascularization procedure prior to amputation; this number remained relatively stable throughout the study period.

Overall, 13% (45/338) had exclusively open treatment and 38% (128/338) had only endovascular interventions before amputation. The proportion of exclusively open treatment decreased substantially, while exclusively endovascular methods were performed increasingly over the years. The highest percentage of patients with only endovascular interventions preceding amputation was seen in 2016 with 64% (14/22) and the lowest in 2002 with 17% (4/23). Exclusively open revascularizations were most prevalent prior to amputation in 2006 with 35% (6/17), while there were no patients with exclusively open interventions amputated in 2013 and 2016. A stable proportion of patients (33%, 112/338) underwent both endovascular and open revascularizations prior to amputation.

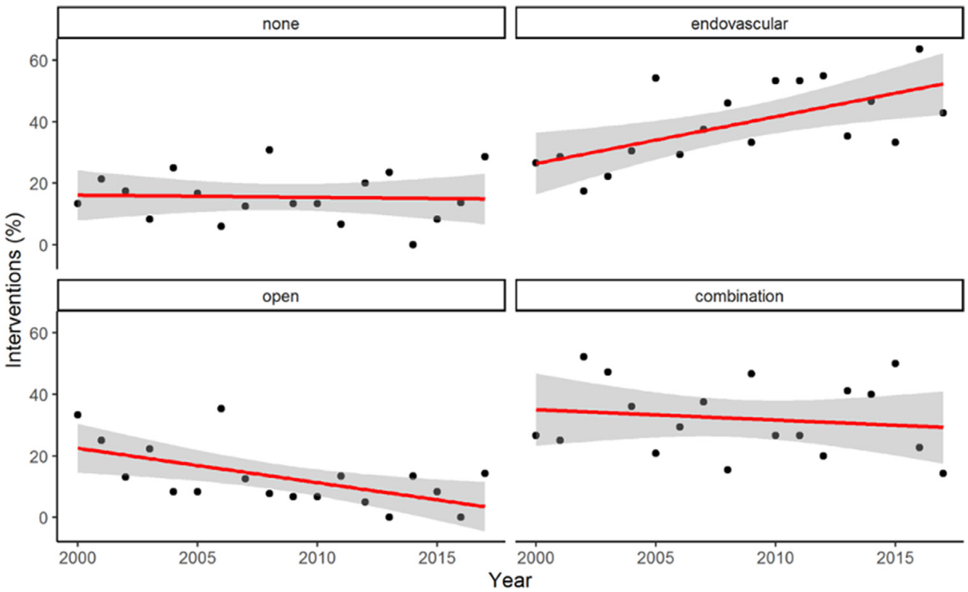

Fig. 2. Revascularization methods prior to major amputation over time (linear fit), including 95% confidence intervals (grey area).

Time to Amputation

Amputation occurred a median of 9.5 months (IQR 0.9-67.6 months) after first ever ipsilateral aortoiliac / femoropopliteal revascularization and 2.1 months (IQR 0.5–13.8 months) after first ever ipsilateral infrapopliteal revascularization ($P < 0.001$) (Fig. 3). Overall, of patients who underwent revascularization, amputation became necessary within 12 months in 61%. Normal linear regression showed no significant change in the time interval between the first revascularization and amputation over the years ($P = 0.887$).

Mortality Rates

The uni- and multivariate analysis showed an association of higher level of amputation and ASA classification with 30-day mortality (Table II). Thirty-day mortality was 8.9% (22/247) after below knee and 27.7% (18/65) after above or through knee amputation; adjusted odds ratio (OR) 3.84 (1.74–8.54), $P < 0.001$. Over the study period a slight increase of mortality with an OR of 1.09 (1.018-1.159) occurred. Kaplan-Meier survival estimates are displayed in Fig. 4.

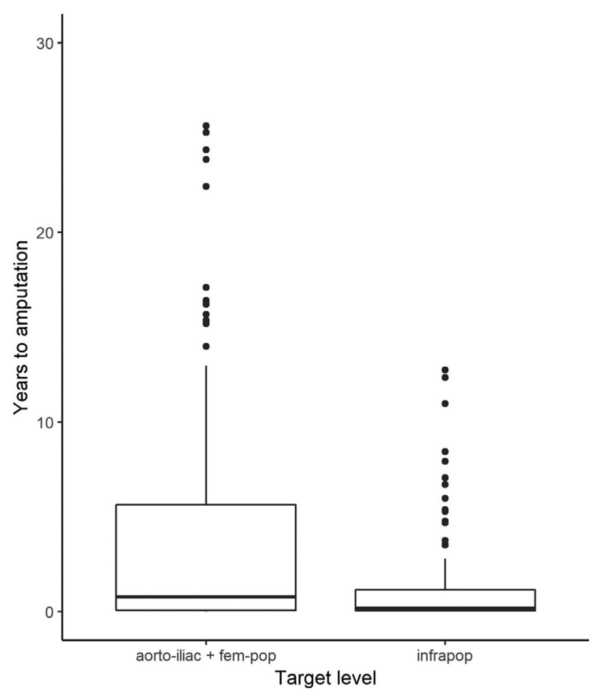

Fig. 3. Years to amputation depending on anatomic revascularization target level.

DISCUSSION

Aim of this study was to assess the type of revascularization prior to and the 30-day mortality rate after major amputation due to PAD over an 18-year period in our hospital.

Over the last 2 decades, we observed an increase in the rates of endovascular procedures and a decrease in open revascularizations. Due to the high prevalence of PAD, industry put a huge effort in developing endovascular innovations. Smaller tools allow revascularization of smaller vessels. Consecutively more revascularization methods are

Table II. Thirty-day mortality depending on amputation level and presence of cardiovascular risk factors

		Deaths	N	%	Adjusted OR	*P* value
Age (10 years)					1.05 (0.75–1.52)	0.766
Sex	female	14	107	13.1	1 (Reference)	
	male	26	205	12.7	1.62 (0.68–4.07)	0.286
Level of amputation	below	22	247	8.9	1 (Reference)	
	through/above	18	65	27.7	3.84 (1.74–8.54)	0.001
Diabetes	no	18	150	12.0	1 (Reference)	
	yes	22	162	13.6	1.22 (0.57–2.67)	0.616
Hypertension	no	14	76	18.4	1 (Reference)	
	yes	26	236	11.0	0.62 (0.28–1.43)	0.255
Dyslipidaemia	no	23	178	12.9	1 (Reference)	
	yes	17	134	12.7	0.95 (0.42–2.13)	0.910
Smoker	no	21	145	14.5	1 (Reference)	
	yes	19	167	11.4	0.68 (0.29–1.58)	0.367
ASA	2 or 3	19	224	8.5	1 (Reference)	
	4	20	85	23.5	2.65 (1.23–5.72)	0.012
Renal insufficiency	no	13	151	8.6	1 (Reference)	
	yes	27	161	16.8	1.76 (0.79–4.07)	0.172
Coronary artery disease	no	16	148	10.8	1 (Reference)	
	yes	24	164	14.6	1.08 (0.49–2.39)	0.848

Renal insufficiency, estimated glomerular filtration rate <60ml/min.
ASA classification, American Society of Anaesthesiologists physical status classification; OR, odds ratio.

Table III. Anatomical distribution of revascularizations prior to amputation

	Mean	SD	Min	25th	Median	75th	Max
n femoropopliteal	1.58	1.96	0	0	1	2	19
n aortoiliac	0.23	0.66	0	0	0	0	4
n infrapopliteal	1.05	1.5	0	0	1	2	11
n any	2.86	2.63	0	1	2	4	19

Mean, SD (standard deviation), Min (minimum), percentiles (25th and 75th) and Max (maximum) are n. a

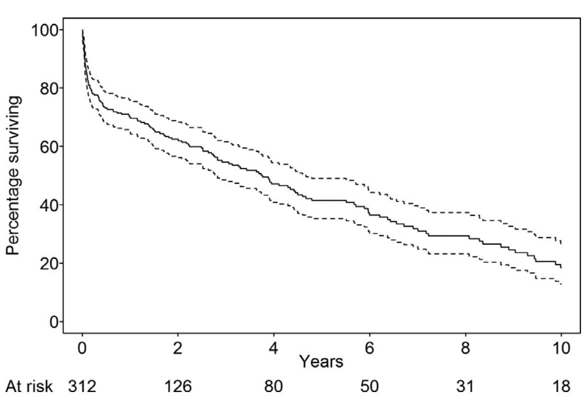

Fig. 4. Kaplan-Meier curve estimating survival including 95% confidence interval bands.

available for increasingly more distal lesions to preserve lower limbs and to delay major amputation as long as possible. Combined intervention methods as well as the number of patients without any revascularization remained stable. In those patients undergoing revascularization, no significant change in the interval from first revascularization to amputation was found over the years.

Similar to our results, Wright et al. found an increase in endovascular procedures by 143% and a decrease in open revascularizations by 35%.[9] In our study, a median of 2 interventions were performed prior to amputation and amputation occurred only 2.1 months after first time infrapopliteal revascularization. This possibly reflects that a more distally located disease leads to earlier amputation. In a Danish population-based cohort study the median time to major amputation was 4.25 months after open surgical revascularization and 5.52 months after endovascular revascularization respectively. Similar to our findings they could determine a mean of 1.5 procedures performed before major amputation occurred.[8] However, distribution patterns of used interventions to maintain limbs have rarely been investigated.

Overall, we observed a slight decrease in major amputations performed due to PAD over the years at our institution. The highest number of amputations were observed in 2002 and 2003 (36 per year) and the fewest were performed in 2017 with only 7 amputations. The multinational study of Behrendt et al. showed decreasing major amputation rates in almost every country, although they noted strong differences among countries, with a mean incidence of major amputation varying between 7.2 and 41.4/100'000.[10] However, yearly numbers of reported amputations in our series are not indicative of the real risk of amputation in the catchment area.

Mortality

Thirty-day mortality was high, especially in patients with a more proximal level of amputation (27.7% for above or through knee amputation). Kelly et al. reported a lower thirty-day mortality rate of 10.3% in transfemoral and only 1.7% in transtibial amputations. [11] In an international context, variable in-hospital mortality rates could be shown. Highest mortality rates were reported in Hungary (20.88%) and lowest in Finland (6.12%).[10] However, the comparison was made without adjusting for other comorbidities. In our univariate and multivariate analysis, mortality was not significantly associated with gender, age, cardiovascular risk factors, coronary artery disease, and renal insufficiency. Only the level of amputation and the presence of a higher ASA classification showed an increased 30-day mortality. These results should be interpreted with care due to the relatively small number of events. But, cardiovascular risk factors, especially arterial hypertension, smoking, coronary artery disease, renal insufficiency, and diabetes were highly prevalent in the cohort. Scott et al. found a significantly increased odds ratio for death in patients older than 74 years.[5]

A well-known reason for PAD is diabetes. A large population based study in Sweden was able to show a 45% relative risk increase of amputation in diabetic patients when compared to non-diabetic patients.[12] Recent results from the EUCLID Trial confirmed diabetes as a risk factor for major amputation in PAD and a 30-day mortality of 6.5 % . [13] These numbers are based on registry data and therefore cannot be compared directly to our results. In our study, 52% of the patients had either type 1 or 2 diabetes, although as mentioned above, this did not influence 30 day mortality, a finding which has also been reported by Lian et al. [14]

Over the observed 2 decades a slight increase in mortality of amputees was noted. These results need to be tempered with caution as there are 2 outlier years with higher mortality (2013 and 2016). Still, in another study a decrease in thirty-day mortality from 10.3% (2000–2002) to 5.1% (2010–2012) was found. [11]

Limitations and Strengths

A limitation of the study is that all patients finally underwent major amputation. PAD patients with revascularization not undergoing major amputation during the study period are not included. Overall incidence of major amputations due to PAD is not available and hence comparability of numbers of amputations is not feasible. Detailed information concerning 30-day mortality was not available. Therefore, this study is not able to give an overall view of trends in peripheral limb revascularization. One of the study's strength are the specific data of anatomical revascularization pattern and frequency of interventions before amputation as well as the large cohort. The long observation period allows for trend analyses but treatment strategies over such a time span are not only influenced by scientific guidelines but also e.g. by availability, reimbursement, and vascular team (surgeons and interventionalists) constellations.

CONCLUSION

Mortality, especially after above/through knee amputation, remains high over the past 2 decades. There is a clear shift towards endovascular treatment of patients with PAD prior to major amputation. In patients needing infrapopliteal revascularizations, amputation was performed much sooner than in those with aortoiliac or femoropopliteal interventions, with no improvement over the years. Strategies to extend limb salvage in these patients should be the focus of further research.

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