Eur J Vasc Endovasc Surg (2019) 58, 729–737

# Major Amputation Rates in Patients with Peripheral Arterial Disease Aged 50 Years and Over in Denmark during the period 1997–2014 and their Relationship with Demographics, Risk Factors, and Vascular Services

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**WHAT THIS PAPER ADDS**

This nationwide study describes the incidence of major amputations of the lower limb caused by peripheral arterial disease and its associations with vascular evaluation and revascularisation during the period 1997–2014. Major amputation rates decreased, but geographic differences in amputation rates were found across the country. Although revascularisation rates increased, very few patients having major amputation had been evaluated by a vascular surgeon, or had been revascularised within the year prior to amputation. No correlation between amputation rates and revascularisations rates were found.

**Objective:** The aim of this nationwide study was to provide insight into the incidence and geographical distribution of vascular services and major amputations in patients with peripheral arterial disease (PAD) in Denmark.

**Methods:** The incidence of major amputation caused by PAD was investigated by linking data from population based healthcare and administrative databases. The study period was divided into three parts, i.e. 1997–2002, 2003–2008, and 2009–2014. Amputation rates and revascularisation rates per 100 000 inhabitants $\geq$ 50 years of age were calculated and the association was displayed using scatter plots. The association between amputation rates and revascularisation rates was explored using a mixed effect model. Multivariable logistic regression was used to identify risk factors for having amputation without prior revascularisation relative to having amputation with prior revascularisation.

**Results:** During 1997–2014, 13 075 first time major amputations were performed. The proportions of patients with diabetes as well as atherosclerotic comorbidity increased through the decades. The incidence rate decreased from 41.67 per 100 000 citizens $\geq$ 50 years of age in 1997–2002, to 32.53 in 2009–2014 ($r = -0.88$, $p < .001$), but with municipal differences. In parallel, revascularisations increased from 166.63 per 100 000 citizens $\geq$ 50 years of age in 1997–2002, to 239.05 in 2009–2014 ($r = 0.83$, $p < .001$). The percentage of patients evaluated by a vascular surgeon within a year prior to amputation increased from 23.7% to 31.3% ($p < .001$), while no increase in the proportion having revascularisation within a year prior to amputation was seen. Multivariable logistic regression analysis showed that diabetes mellitus (OR 1.28; CI 1.17–1.40), stroke (OR 1.66; CI 1.52–1.81), coronary heart disease (OR 1.25; CI 1.14–1.37), and renal disease (OR 1.31; CI 1.15–1.48) were associated with a higher risk of undergoing amputation without prior revascularisation.

**Conclusions:** The incidence of major amputations decreased, while general cardiovascular prevention and revascularisation rates increased. Despite that, few patients had revascularisation prior to amputation, leaving room for improvements.

**Keywords:** Major amputation, Major amputation rates, Peripheral arterial disease, Revascularisation rates
Article history: Received 18 November 2018, Accepted 11 June 2019, Available online 21 September 2019


## INTRODUCTION

Peripheral arterial disease (PAD) is an important healthcare problem and when severe, it can cause critical limb ischaemia and lead to major amputation. Despite advances in surgical and endovascular revascularisation procedures,

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https://doi.org/10.1016/j.ejvs.2019.06.007

PAD is associated with 53—90% of all major amputations of the lower limb.[1]

A decrease in lower limb amputations has been described in different countries.[2,3] Whether the decrease in amputation rates can be attributed only to better preventive care or to the increased rate of revascularisation performed is unknown.[4]

Variations in major amputation rates across communities have been shown within countries with private health insurance[5] and in countries with a public health service.[6] Such variation might be caused by socio-economic differences[7] or might reflect important geographical differences in healthcare structure.[8]

In a previously published study[9] the risk of major amputation after revascularisation was explored, using information originating from the same set of data used in this study. While the previous study sought to explore the risk of major amputation in already revascularised patients this study aimed to explore the population based incidence of PAD related major amputation and the potential associations to risk factors, comorbidities, and the current practice of vascular services including revascularisation. Furthermore, the existence of geographic differences was investigated and the potential relationship with different revascularisation rates was explored.

## MATERIALS AND METHODS

The incidence of major limb amputation caused by PAD in Denmark is described using data from the population based healthcare and administrative databases.

The Danish population is provided with taxpayer supported healthcare by the Danish National Health Service and is allowed free access to hospitals, general practitioners, rehabilitation, and the reimbursement of some expenses of prescribed drugs, including secondary medical preventive treatment. Each citizen receives a unique civil registration number enabling individual linkage between population based administrative and healthcare registries.[10]

Information was obtained from the Civil Registration System, The Danish National Patient Registry, The Danish Vascular Registry, The Danish National Prescription Registry, The Integrated Database for Labour Marked Research Agency, and Statistic Denmark. Data on population size was obtained from Statistic Denmark.

The project was approved by the Danish Data Protection Agency. Data for analysis were anonymised, and therefore no patient informed consent was required according to Danish legislation.

### Study population

A dataset containing all patients undergoing major amputation between 1 January 1997 and 31 December 2014 was extracted from the Danish National Patient Registry (Fig. 1), which contains information on all hospital admissions and contacts with outpatient clinics. Diagnostic coding is recorded using the International Classification of Diseases (ICD-10)[11] and surgical procedures are coded according to the Scandinavian classifications of surgical and other procedures (NOMESCO).[12] The Danish National Patient Registry is considered to have high validity for a range of diagnoses, including PAD.[13]

Major amputation was defined as an amputation above the ankle joint, corresponding to NOMESCO[12] procedure codes KNFQ09, KNFQ19, KNFQ99, KNGQ09, KNGQ19, and KNGQ99. Patients $\geq$ 50 years of age with a primary or secondary PAD diagnosis (including arterial emboli and/or thrombosis in the lower limb), related to major amputation were included. Age $\geq$ 50 years was chosen as the cutoff because PAD is uncommon in younger patients. Diagnostic codes were I70, I702, I709, I739, I74, I740, I741, and I743 — I749. It is not possible to gain information on onset of PAD symptoms in the Danish patient Registry, and therefore

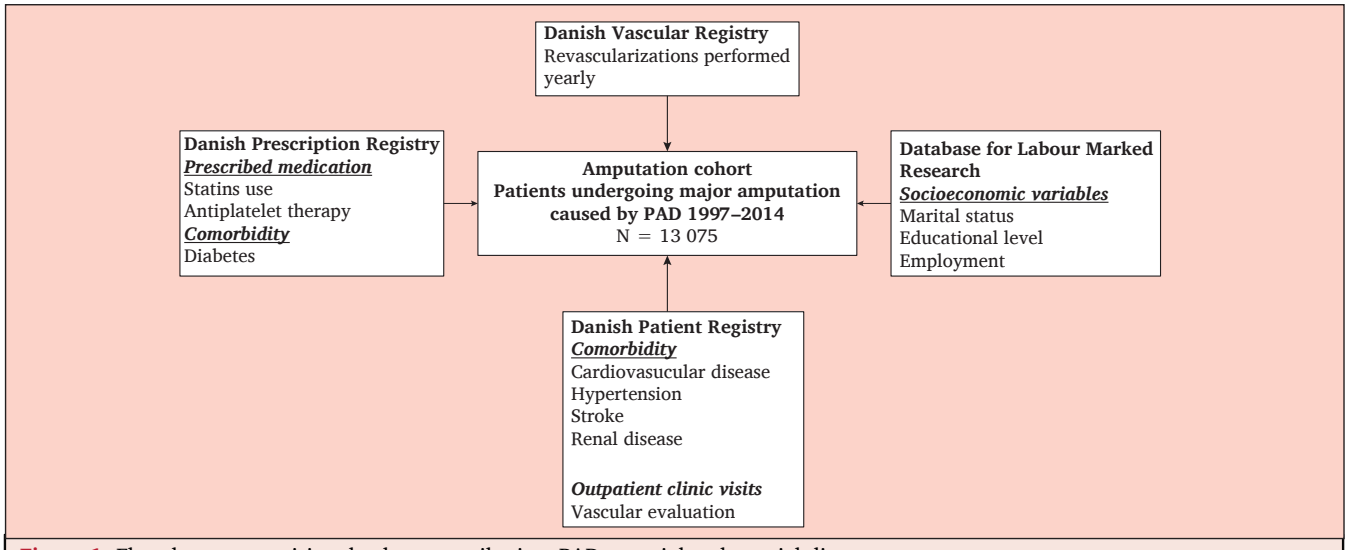


**Figure 1.** Flowchart summarising database contribution. PAD = peripheral arterial disease.

amputation could be caused by either chronic or acute limb ischaemia. If a patient had more than one major amputation during the study period, only data concerning the primary major amputation were used.

### *Vascular services including revascularisation*

To provide an insight into vascular assessment and attempted revascularisation prior to major amputation, PAD diagnoses and procedure codes relating to surgical and interventional revascularisation procedures were identified cross linking information from the Danish Vascular Registry and the Danish Patient Registry (Supplementary material, Appendix I). Information was collected for five years prior to the date of major amputation. If patients had had more than one revascularisation preceding a major amputation the earliest revascularisation was used as the index procedure. Information on outpatient visits was also extracted from the Danish Patient Registry, and was defined as a visit to a vascular outpatient clinic prior to amputation, if the visit had a PAD diagnosis coding. An outpatient visit included a vascular evaluation with pulse palpation, ankle brachial index measurement, toe pressure measurement, and vascular imaging if indicated.

### *Comorbidity and prescribed medication*

Data on patient comorbidity and prescribed medication were obtained from The Danish Patient registry, and the Danish National Prescription Registry. The comorbidity variables; coronary artery disease (I20 — 25), hypertension (I10 — 15), stroke and transient ischaemic attack (I63 — I67 and G45), and renal insufficiency (N18 — 19) were extracted from The Danish Patient registry using the corresponding ICD codes. Diabetes was defined according to prescribed medication. A patient was given the diagnosis of diabetes if they had received anti-diabetic medication in the year prior to revascularisation. Information about statins and antiplatelet therapy was extracted from the Danish National Prescription Registry in the same way. Data on smoking habits are not recorded in the registries and are therefore unknown for patients in this study.

### *Demographics*

The Integrated Database for Labour Marked Research retains yearly updated information on socio-economic status for the entire Danish population. The registry contains information on gross income, educational level, employment status, and marital status.

Patients were classified according to marital status (yes/no), employment (employed, retired, missing data), and educational level (Primary or lower secondary school, upper secondary and vocational education, higher education, or missing data).

### *Population data*

The political and administrative system in Denmark underwent a reform on 1 January 2007 when the existing 14 counties and 270 municipalities were re-organised into five regions and 98 larger municipalities. To be able to compare incidence rates and explore differences in the same geographic area over time, the study period was divided in three periods (1997—2002, 2003—2008, and 2009—2014) and the municipalities from before 2007 were merged into larger units constituting the 98 municipalities established in 2007. Patients were allocated the municipality were they lived on the day of amputation. Each municipality was allocated to the catchment area of the local centre of vascular surgery in order to explore whether the impact of revascularisation on major amputations differed across the country. Each vascular centre has a unique catchment area following the municipal borders.

Incidence rates for amputation used data from the Danish Patient Registry as numerator with the denominator population derived from Statistic Denmark. Yearly numbers of revascularisation procedures performed were collected from the Danish vascular registry and used as numerator for calculation of incidence rates for revascularisation with the denominator population derived from Statistic Denmark. Numbers on population $\geq$ 50 years of age were obtained yearly on a national and a municipal level (determined from the midyear census estimate).

### *Statistics*

Descriptive statistics of baseline characteristics for each time period were performed. Employment and education was the only variables with missing data. Missing data were treated as an independent group within the variables. To test for differences between patients with and without prior revascularisation in each period the Wilcoxon rank sum test was used for continuous variables and Pearson's chi-square test for categorical variables. Multivariable logistic regression was performed to determine risk factors associated with amputation without prior revascularisation relative to amputation with prior revascularisation. Baseline characteristics were: age, gender, comorbidity (hypertension, coronary artery disease, stroke, diabetes, and renal disease), prescribed statins and platelet inhibitors at time of amputation, marital status, and educational level. Odds ratios (ORs) and 95% confidence intervals (CIs) were provided for each time period.

Amputation rates per 100 000 citizens $\geq$ 50 years of age were calculated on a national and municipal level for each time period using the combined number of major amputation as the numerator and the combined population numbers $\geq$ 50 years of age as denominator. The association between time periods and municipal amputation rates was explored using Pearson's correlation. Revascularisation rates per 100 000 citizens $\geq$ 50 years of age were calculated on a national and municipal level for each time period using the combined number of revascularisations as the numerator and the combined population numbers $\geq$ 50 years of age as denominator.

The association between municipal revascularisation rates and amputation rates was examined for each time

period using scatter plots and correlation coefficients were calculated. To explore the impact of revascularisation rates on amputation rates over time at a municipal level, a mixed effect model with random slope (allowing each municipality to have a unique change in amputation rates) and random intercept (allowing each municipality to have a unique overall level) was fitted. Initial analysis was done including revascularisation rate, the three time periods, and the interaction between revascularisation rate and time period, assuming random effect of municipalities. Municipal revascularisation rates were defined as the proportion of revascularisations performed in the year of amputation.

Municipalities were merged into larger units corresponding to each vascular catchment area. Amputation rates and revascularisation rates were calculated to explore whether differences existed. Multivariable logistic regression was used to determine whether different revascularisation rates were associated with differences in undergoing amputation without prior revascularisation relative to amputation with prior revascularisation.

Both statistical analyses and mapping were performed using STATA/IC 14.1, (Houston, Texas, USA).

## RESULTS

In 1997–2014, a total of 24 576 major amputations were performed (94.3% in patients $\geq$ 50 years). A total of 16 034 (69.2%) PAD related major amputations were performed in patients $\geq$ 50 years of age and first time major amputations accounted for 13 075 (81.5%). A significant decrease in the overall incidence of major amputations was observed from 41.67 per 100 000 citizens $\geq$ 50 years of age in 1997–2002, to 37.95 in 2003–2008, and 32.53 in 2009–2014 ($r = -0.88$, $p < .001$). The below knee/above knee ratio almost halved due to increased numbers of above knee amputations from 1.14 in 1997–2002 to 0.95 in 2003–2008 and 0.65 in 2009–2014 ($p < .001$) (Table 1).

### *Baseline characteristic*

Table 1 shows the characteristics of patients having major amputation. In all three time periods more men than

**Table 1. Demographics and clinical characteristics of patients with major amputation caused by PAD**

| | Total | 1997–2002 | 2003–2008 | 2009–2014 |
|---|---|---|---|---|
| *n* | 13 075 | 4 645 | 4 365 | 4 065 |
| Age, years, mean (SD) | 75.80 (10.2) | 75.39 (10.0) | 76.09 (10.2) | 75.96 (10.5) |
| Male sex | 7 152 (54.7) | 2 523 (54.3) | 2 350 (53.8) | 2 279 (56.1) |
| *Comorbidity* | | | | |
| Hypertension | 10 611 (81.2) | 3 576 (77.0) | 3 651 (83.6) | 3 384 (83.3) |
| Coronary artery disease | 4 231 (32.4) | 1 285 (27.7) | 1 577 (36.2) | 1 369 (33.7) |
| Stroke | 3 912 (29.9) | 1 293 (27.8) | 1 369 (31.4) | 1 250 (30.8) |
| Diabetes | 3 820 (29.2) | 1 319 (28.4) | 1 245 (28.5) | 1 256 (30.9) |
| Renal disease | 1 420 (10.9) | 317 (6.8) | 507 (11.6) | 596 (14.7) |
| *Medication* | | | | |
| Statins | 3 790 (29.0) | 233 (5.0) | 1 387 (31.8) | 2 170 (53.4) |
| Platelet inhibitors | 7 632 (58.4) | 2 187 (47.1) | 2717 (62.3) | 2 728 (67.1) |
| *Marital status* | | | | |
| Married | 4 983 (38.1) | 1 840 (39.6) | 1627 (37.3) | 1 516 (37.3) |
| Un-married | 8 092 (61.9) | 2 805 (60.4) | 2738 (62.7) | 2 549 (62.7) |
| *Employment* | | | | |
| Employed | 395 (3.0) | 124 (2.7) | 152 (3.5) | 119 (2.9) |
| Pensioner | 12 474 (95.4) | 4 460 (96.0) | 4 154 (95.2) | 3 860 (95.0) |
| Other | 206 (1.6) | 61 (1.3) | 59 (1.4) | 86 (2.1) |
| *Education level* | | | | |
| Primary and lower secondary school | 5 831 (44.6) | 1 712 (36.9) | 2 031 (46.5) | 2 088 (51.4) |
| Upper secondary school and vocational education | 3 033 (23.2) | 764 (16.5) | 1 039 (23.8) | 1 230 (30.3) |
| Higher education | 856 (6.6) | 225 (4.8) | 286 (6.6) | 345 (8.5) |
| No information | 3 355 (25.7) | 1 944 (41.9) | 1 009 (23.1) | 402 (9.9) |
| *Amputation level* | | | | |
| Above knee | 6 881 (52.6) | 2 169 (46.7) | 2 241 (51.3) | 2 471 (60.8) |
| Below knee | 6 194 (47.4) | 2 476 (53.3) | 2 124 (48.7) | 1 594 (39.2) |
| Below knee/above knee ratio | 0.90 | 1.14 | 0.95 | 0.65 |
| *Seen in outpatient clinic* | | | | |
| Yes | 3 622 (27.7) | 1 100 (23.7) | 1 250 (28.6) | 1 272 (31.3) |
| *Prior revascularisation* | | | | |
| Yes | 4 391 (33.6) | 1 455 (31.3) | 1 446 (33.1) | 1 490 (36.7) |
| *Endovascular procedures* | 1 371 (31.2) | 282 (19.4) | 427 (29.5) | 662 (44.4) |
| $\leq$1 year | 3 069 (23.5) | 1 096 (23.6) | 966 (22.1) | 1 007 (24.8) |
| <30 days | 1 483 (11.3) | 502 (10.8) | 483 (11.1) | 498 (12.3) |

Data are presented as *n* (%) unless stated otherwise. PAD = peripheral arterial disease; SD = standard deviation.

women had major amputation and men were younger than women at the time of amputation: 73.47 (SD 10.01) *vs.* 78.62 (SD 9.75) years, $p < .001$. Overall mean age at the time of amputation increased significantly, while mean age for men did not change. The mean age for women rose by 1.48 years ($p < .001$).

### Comorbidity and secondary medical prevention

Hypertension was the most common risk factor, increasing from 77.0% in 1997–2002 to 83.3% in 2009–2014. Coronary artery disease and previous stroke also became more common. Significantly more men than women had coronary artery disease (36.5% *vs.* 27.3%). This was also true for the prevalence of previous stroke (56.2% *vs.* 43.8%).

An increase in the prevalence of diabetes was seen between 2003 – 2008 (28.5%) and 2009–2014 (30.9%) ($p = .02$), while no difference was found between 1997 – 2002 (28.4%) ($p = .91$). Patients with diabetes were younger (73.7 years *vs.* 76.7 years), $p < .001$) than patients with no diabetes, and men were younger than women (71.9 years *vs.* 76.6 years, $p < .001$). Most patients with diabetes were men (62.1%) and during the study period the proportion of men having diabetes increased ($p < .001$) while no increase in the proportion of women with diabetes was seen ($p = .34$).

The use of both anti-platelet therapy and statins significantly increased during the study period ($p < .001$ for both) (Table 1).

Multivariable analysis of patient characteristics showed that increasing age and known comorbidity were associated with increasing risk of being amputated without prior attempted revascularisation (Table 2).

**Table 2. Multivariable logistic regression analysis identifying risk factors associated with undergoing major amputation without attempted revascularisation relative to amputations with prior attempted revascularisation ($n = 13\,075$)**

| Variable | OR | CI 95% | *p* value |
|---|---|---|---|
| *Period* | | | |
| Per one period increase | 0.87 | 0.82–0.92 | <.001 |
| *Age, years* | | | |
| 50–59 (ref.) | 1 | | |
| 60–69 | 1.07 | 0.91–1.24 | .41 |
| 70–79 | 1.47 | 1.26–1.70 | <.001 |
| 80–89 | 2.13 | 1.81–2.51 | <.001 |
| ≥90 | 3.63 | 2.83–4.66 | <.001 |
| *Sex* | | | |
| Female (ref.) | 1 | | |
| Male | 1.02 | 0.94–1.11 | .66 |
| *Comorbidity* | | | |
| Hypertension | 0.92 | 0.85–1.01 | .07 |
| Coronary heart disease | 1.25 | 1.14–1.37 | <.001 |
| Stroke | 1.66 | 1.52–1.81 | <.001 |
| Diabetes | 1.28 | 1.17–1.40 | <.001 |
| Renal disease | 1.31 | 1.15–1.48 | <.001 |
| *Medication* | | | |
| Statins and platelet inhibitors | 0.59 | 0.54–0.65 | <.001 |
| *Marital status* | | | |
| Un-married (ref.) | 1 | | |
| Married | 0.81 | 0.75–0.88 | <.001 |
| *Education level* | | | |
| Primary and lower secondary school (ref.) | 1 | | |
| Upper secondary school and vocational education | 0.93 | 0.85–1.02 | .14 |
| Higher education | 0.92 | 0.80–1.08 | .34 |
| No information | 1.21 | 1.06–1.38 | .004 |

CI = confidence interval; OR = odds ratio.

### Amputations and revascularisation

The incidence of major amputations decreased at a national level, but differences between municipalities were seen in all three time periods (Fig. 2). The difference per 100 000 citizens ≥ 50 years of age was 15.68–80.33 in 1997–2002, 15.24–105.65 in 2003–2008, and 9.32–58.67 in 2009–2014.

The number of revascularisations performed each year increased significantly. The national incidence per 100 000 citizens ≥ 50 years of age rose from 166.63 in 1997–2002, to 228.82 in 2003–2008, and 239.05 in 2009–2014 ($R = 0.83$, $p < .001$).

Patients being evaluated by a vascular surgeon within one year prior to amputation increased significantly during the study period, (23.7%, 28.6%, and 31.3%, respectively, $p < .001$). Despite this increase, no change in the proportion of patients revascularised within one year prior to amputation was found (23.6%, 22.1%, and 24.8%, respectively, $p = .23$).

### Impact of revascularisation

The association between revascularisation rate and amputation rate on a municipal level showed a positive correlation, although only significant in 2003–2008 ($R = 0.33$, $p < .001$) (Fig. 3A–C). When fitting the random mixed effect model no association was found between changes in amputation rates and changes in revascularisations rates, at a municipal level over time ($p = .97$), meaning that increasing revascularisation rates could not be associated with decreasing amputations rates within municipalities.

Municipalities were then merged into seven larger units corresponding to the vascular centre catchment areas to explore differences between these areas. Table 3 shows the amputation and revascularisation rates for each vascular catchment area.

Multivariable analysis of patient characteristics, and revascularisation rates, showed no obvious difference in the risk of being amputated without prior attempted revascularisation between living in a catchment area with low revascularisation activity compared with a catchment area with high activity (Table 4).

## DISCUSSION

This nationwide study described the incidence of major amputations of the lower limb caused by PAD and its associations with vascular evaluation and revascularisation.

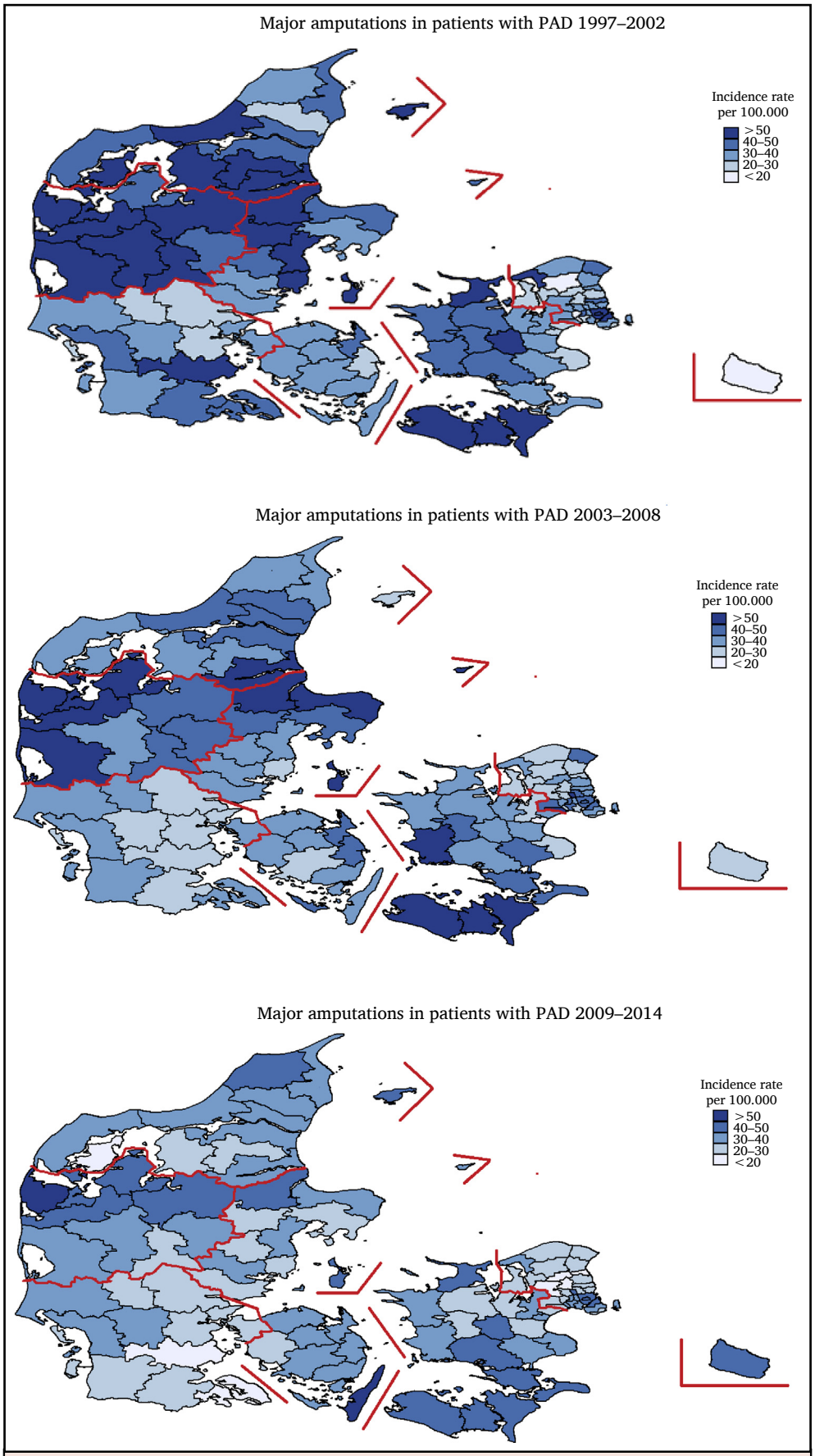


**Figure 2.** Incidence rates for major amputation for each time period. Red lines indicate borders of catchment areas. PAD = peripheral arterial disease.

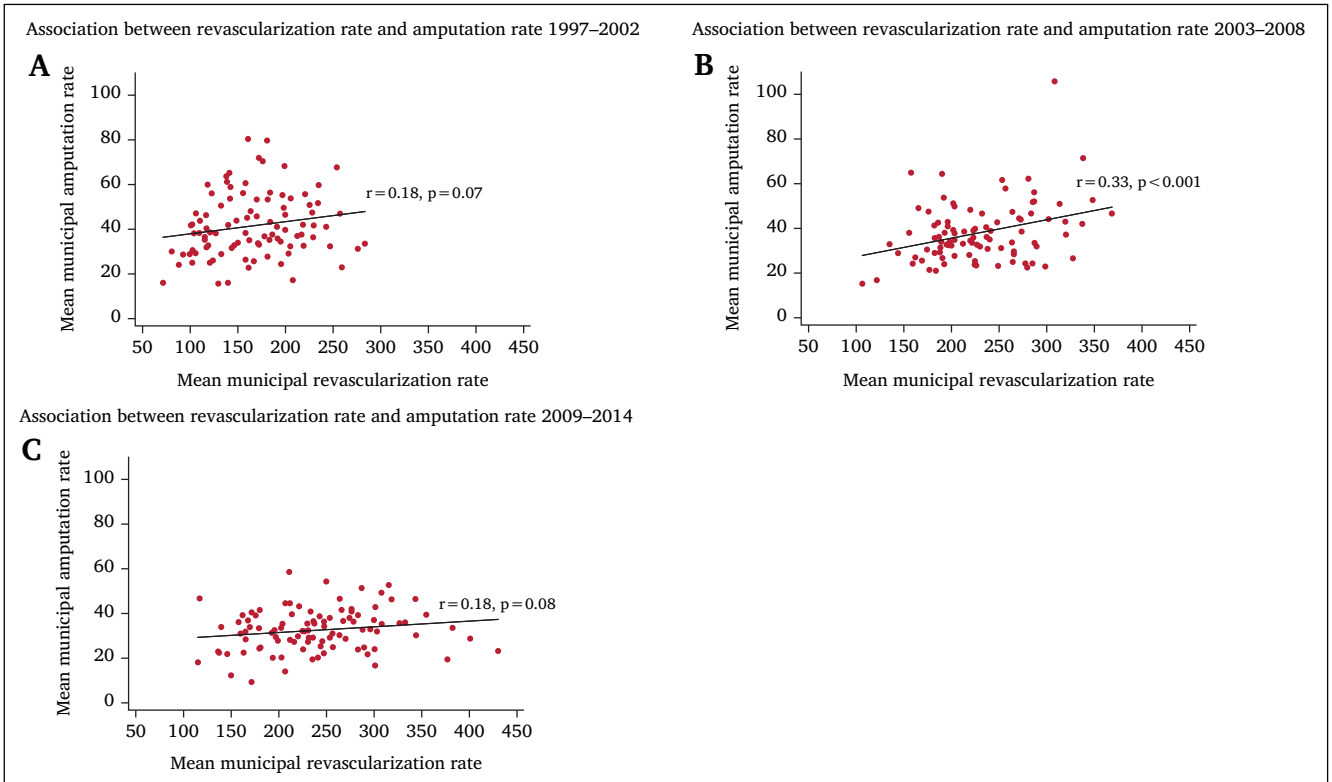


**Figure 3.** Correlation at the municipal level is shown for each time period between revascularization rate and amputation rate. Mean amputation rate and revascularization rate is per 100 000 inhabitans ≥ 50 years of age.

PAD related amputations counted for 69.2% of all major amputations, and like others,[14] it was found that the incidence of major amputations decreased during the study period, although differences in amputation rates were found across the country. Revascularisation rates increased but only 24%—31% of patients having major amputation were evaluated by a vascular surgeon and only 25% had revascularisation within the year prior to amputation. This seemed similar in all catchment areas regardless of their amputation and revascularisation incidences.

### *Comorbidity and secondary medical treatment*

Hypertension, coronary artery disease, and stroke increased significantly during the study period, which could have been due to increased awareness of cardiovascular disease, and for patients with hypertension, change in recommendations regarding target blood pressure during the study period. The increasing use of both statins and anti-platelet therapy during the study period adds to this assumption. However almost half of patients did not take statins and almost one third did not receive anti-platelet therapy. This lack of

**Table 3. Amputation and revascularisation rates for each vascular catchment area**

| Catchment area | 1997–2002 | | | 2003–2008 | | | 2009–2014 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Population ≥50 years | Rate per 100 000[a] | | Population ≥50 years | Rate per 100 000[a] | | Population ≥50 years | Rate per 100 000[a] | |
| | | Major amp. | Re-vasc. | | Major amp. | Re-vasc. | | Major amp. | Re-vasc. |
| Copenhagen | 544 860 | 33.94 | 169.36 | 542 501 | 34.23 | 221.51 | 570 177 | 27.67 | 196.66 |
| Odense | 162 525 | 35.31 | 168.01 | 174 392 | 37.25 | 218.40 | 187 290 | 37.31 | 205.51 |
| Kolding | 233 027 | 36.13 | 170.59 | 251 655 | 28.97 | 252.45 | 272 907 | 27.17 | 337.59 |
| Slagelse | 279 339 | 40.89 | 117.10 | 304 381 | 38.52 | 199.79 | 328 131 | 34.73 | 282.28 |
| Aarhus | 211 609 | 48.35 | 197.86 | 232 698 | 48.36 | 198.86 | 254 906 | 33.18 | 178.34 |
| Aalborg | 198 575 | 51.90 | 192.51 | 210 740 | 36.23 | 258.97 | 224 857 | 33.90 | 242.57 |
| Viborg | 161 043 | 62.41 | 178.30 | 175 937 | 52.23 | 283.63 | 192 391 | 43.47 | 263.01 |
| p value[b] | | <.001 | <.001 | | <.001 | <.001 | | <.001 | <.001 |
| Total | 1 790 978 | 41.65 | 166.63 | 1 892 304 | 37.96 | 228.82 | 2 030 659 | 32.53 | 239.05 |

[a] Major amputation (Major amp.) rates and revascularisation (Re-vasc.) rates are based on population ≥50 years of age.
[b] Non-parametric test for difference in rates per 100 000 between catchment areas.

**Table 4. Multivariable logistic regression model identifying the impact of intensity of revascularisation associated with undergoing amputation without an attempt at revascularisation**

| Revascularisation rate by catchment area[a] | 1997–2002 | | | 2003–2008 | | | 2009–2014 | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | CI 95% | *p* value | OR | CI 95% | *p* value | OR | CI 95% | *p* value |
| 1 lowest (ref) | 1 | | | 1 | | | 1 | | |
| 2 | 0.61 | 0.45–0.83 | .001 | 1.29 | 1.01–1.65 | .04 | 1.22 | 0.96–1.54 | .10 |
| 3 | 0.66 | 0.53–0.83 | .001 | 1.06 | 0.80–1.42 | .70 | 1.03 | 0.78–1.37 | .85 |
| 4 | 0.66 | 0.50–0.86 | .002 | 1.05 | 0.84–1.31 | .64 | 0.64 | 0.49–0.83 | <.001 |
| 5 | 0.80 | 0.61–1.04 | .09 | 0.89 | 0.67–1.68 | .39 | 0.70 | 0.53–0.91 | .007 |
| 6 | 0.59 | 0.46–0.77 | <.001 | 0.74 | 0.57–0.96 | .02 | 1.05 | 0.82–1.34 | .73 |
| 7 highest | 0.61 | 0.47–0.79 | .001 | 1.10 | 0.85–1.44 | .47 | 0.46 | 0.35–0.59 | <.001 |

[a] Listed according to revascularisation rates for each period, Table 3. OR = odds ratio; CI = confidence interval.

sufficient treatment has been reported by others,[15] even though current guidelines for the management of patients with PAD recommend aggressive lipid lowering therapy with a statin and anti-platelet therapy.[16]

The proportion of patients having diabetes at the time of major amputation slightly increased during the study period. From the data it was not possible to examine amputations rates in patients with diabetes separately as there is information on patients having both PAD and diabetes, but not on patients with diabetes only. However a recent Danish study has shown a decrease in major amputations in patients with diabetes.[17] These two results do not contradict one another, but probably reflect the increasing prevalence of diabetes in the Danish population and an improvement in diabetic care.

### Revascularisation

It has been suggested that revascularisation lowers the amputation level, but it was found that above knee amputations increased leading to a shift towards more above knee than below knee amputations. Higher rates of above knee than below knee amputations have been reported by others. In a study from the UK[18] a below knee—above knee ratio 0.93 in 2003—2008 was reported corresponding to the findings here over the same period (0.95), while Kolossvary et al.[19] found that only 27% of major amputations in Hungarian PAD patients were below knee amputations. Revascularisation rates in Denmark increased, but no change in the proportion of patients with revascularisation within one year prior to amputation was seen. The reason for this high proportion of patients not having any vascular service prior to amputation is unclear, but could be due to unawareness of symptoms, and perhaps also lack of knowledge about vascular reconstruction opportunities, in public[20] as well as in health professionals,[21] leading to "too late" presentation of symptoms. Underutilisation of revascularisation as a potential cause of major amputation has been reported,[14,19] although international recommendations for revascularisation for limb salvage in PAD exist.[16] This could be one of the explanations why more patients are having amputations above knee instead of below knee and why it is crucial to draw attention to the importance of vascular evaluation prior to major amputation for ischaemia.

### Geographical variations

The incidence of major amputations across Denmark varied, and no correlation between revascularisation and amputation rates was found in the three periods. The revascularisation rate varied between catchment areas and was almost twice as high in the catchment area with the lowest amputation rate compared with the area with the highest amputation rate. This could suggest that higher revascularisation rates are associated with lower amputation rates. However, in the last period, the area with the lowest amputation rate had the highest rate of vascular reconstructions, but the area with the second lowest amputation rate also had one of the lowest revascularisation rates indicating that differences in amputation rates cannot be explained by more revascularisation alone. Differences between socio-economic factors and distribution of risk factors for PAD are obvious explanations and should be further investigated.

### Strengths and limitations

The strength of this study is its population based design and the possibility to combine several national registries. In the set up, all major amputations were identified for an 18 year period, and it was possible to link the event with diagnoses, prior medical history, prescribed medication, and socio-economic information at an individual level. The validity of estimates depends on the accuracy of the data used. The accuracy of the Danish Vascular Registry has been described as good.[22] In the Danish Patient Registry the predictive value for a wide range of diagnoses has been reported to be high including PAD diagnoses in hospitalised patients,[13,22] although the possibility of coding errors cannot be entirely excluded.

One limitation is the lack of smoking data. Smoking in the general population has declined, and in 2013 18.9% smoked daily.[23] Whether smoking has declined similarly in this cohort is unknown, but it is believed that the proportion of smokers is higher than the general population. In a recent study of PAD patients having revascularisation the proportion of daily smokers was 45.4%.[9] Although the two PAD cohorts are not directly comparable it is believed that the proportion of smokers is higher in this study than in the

general population as well. Another limitation was the use of written prescriptions as a surrogate for actual drug use. It was not certain that the patients actually took the drugs, although the fact that they paid a part of the drug expenses out of their own pocket does indicate that a written prescription is likely to reflect actual drug use. No information about amputation preventive care such as podiatric visits, wound care, diabetes monitoring, or visits to general practitioners was available. All these factors might play an important role in the prevention of amputation and differ from catchment area to catchment area due to structural differences in healthcare delivery.

## CONCLUSION

The incidence of major amputations caused by PAD decreased during the period 1997 to 2014, while revascularisation rates increased. Despite this, vascular evaluation prior to amputation only increased slightly, while no change in patients revascularised within a year prior to amputation was seen, leaving room for improvements.

## FUNDING

Louise S. Londero has received scholarships from The Danish heart association, Region of Southern Denmark, and University of Southern Denmark.

## CONFLICTS OF INTEREST

None.

## APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2019.06.007.

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