BMJ Open

Progression of disease preceding lower extremity amputation: A longitudinal registry study of diagnoses, use of medication and healthcare services 14 years prior to amputation

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016030
Article Type:	Research
Date Submitted by the Author:	25-Jan-2017
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Primary Subject Heading:	Health services research
Secondary Subject Heading:	Diabetes and endocrinology, Epidemiology, Cardiovascular medicine
Keywords:	Lower extremity amputation, Atherosclerosis, Diabetes, Healthcare service

Title

Progression of disease preceding lower extremity amputation: A longitudinal registry study of diagnoses, use of medication and healthcare services 14 years prior to amputation

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Word count: 3951

Abstract

Objectives: Patients with non-traumatic lower extremity amputation are characterised by high age, multi-morbidity and polypharmacy and long term complications of atherosclerosis and diabetes. To ensure early identification of patients at risk of amputation, we need to gain knowledge about the progression of diseases related to lower extremity amputations during the years preceding the amputation.

Design: A population-based national registry study.

Setting: The study includes data on demographics, diagnoses, surgery, medications, and healthcare services from five national registries. Data were retrieved from 14 years before until 1 year after the amputation. Descriptive statistics were used to describe progression of diseases and use of medication and healthcare services.

Participants: An unselected cohort of patients (≥50 yrs; n=2883) subjected to a primary non-traumatic lower extremity amputation in 2010 or 2011 in Denmark.

Results: The prevalence of atherosclerosis, hypertension and diabetes was 70%, 53% and 49%, respectively. Among patients with atherosclerosis, 42 % had not received cholesterol-lowering treatment even though 87% had visited their general practitioner within the last year prior to amputation. Further, 16% were diagnosed with diabetes at the time of the amputation. The prevalence of cardiovascular diseases increased from 22% to 70%, atherosclerosis from 5% to 53%, and diabetes from 17% to 35% over the 14 years preceding major amputation. Of all patients, 64% had been in contact with the hospital or out-patient clinics within the last three years and 34% had received a prescription of opioids within the last year prior to the amputation.

Conclusion: Among patients with non-traumatic lower extremity amputation, one third live with undiagnosed and untreated atherosclerosis and one sixth suffer from undiagnosed diabetes despite continuous contacts to general practitioner and the hospital. This study

emphasizes a need for enhanced focus, among both hospital clinicians and general practitioners, on the early identification of atherosclerosis and diabetes.

Keywords Lower extremity amputation, Atherosclerosis, Diabetes, Healthcare services

Article Summary

Article focus

- Patients who undergo non-traumatic lower extremity amputation (LEA) are characterised by high age, multi-morbidity, polypharmacy and high mortality.

- To ensure early identification of patients at risk of LEA, we need to gain more knowledge about the development and progression of LEA-related diseases.

Key messages

- One third of patients with LEA were living with undiagnosed and untreated atherosclerosis and one out of six were living with undiagnosed diabetes despite regular contact with their GPs and outpatient clinics for several years prior to amputation

- Atherosclerosis is the primary comorbidity among patients undergoing major extremity amputations. For the majority of patients, the major LEA is a first-time amputation.

- Clinicians are encouraged to supplement medical treatment of cardiovascular diseases, including pain treatment, with a careful inspection of the patient´s feet as this non-invasive examination may detect insufficient circulation.

Strengths and limitations of the study

- The strengths of this national registry study were the inclusion of data describing diagnoses and use of medication and healthcare services during the last 14 years preceding non-traumatic LEA performed in Denmark.

- The main limitation was the lack of a control group. An age-, sex-, and geographically-matched control group would have allowed differentiation between disease progression due to aging and disease progression leading to amputation. An inherent limitation was that the data did not allow an estimation of patient compliance with the prescribed medication.

Abbreviations

LEA: lower extremities amputation

Major LEA: Lower extremity amputation performed above the ankle level

Minor LEA: Lower extremity amputation performed below the ankle level

AKA: Above knee amputation

BKA: Below knee amputation

PAD: Peripheral artery disease

GP: General practitioner

Introduction

Lower extremity amputation (LEA) is a severe event associated with loss of mobility, pain, decreased quality of life, major disfigurement, and increased risk of re-amputation and hospitalisation (1–3). Even though the incidence of LEA has decreased worldwide over the last two decades, large variations persist; from 5.8 to 31 per 10^5 individuals in different populations (4). Moreover, the reported one-year mortality rate was 12% to 58% (5–8), and the highest mortality rate (45% -58%) was associated with above-the-knee amputations (AKA) (9,10). Age and the severity of comorbidities are the most prominent prognostic factors for mortality after LEA (6,7).

The most prevalent comorbidities in patients with LEA are atherosclerosis and diabetes (4,11,12). Among all major amputations, approximately 50-90% are related to peripheral artery disease (PAD), 20-80% are related to diabetes, and 10% to trauma (13). During the last decade, the global prevalence of PAD has increased by 23%, with the highest increase among low-income countries (14). The risk factors for PAD are age, smoking, history of cardiovascular diseases, diabetes, hypertension, dyslipidaemia, and obesity (15). To our knowledge, only one previous study has investigated the progression of LEA-related diseases by examining the use of medication over a seven-year period prior to amputation among patients diagnosed with diabetes (16). Buckley et al. recommended an earlier referral to a medical specialist to prevent LEA. Currently, the estimated global prevalence of diabetes is 9% and 90% is characterised as type 2 diabetes (17). Furthermore, the prevalence of diabetes is estimated to increase by 55% over the next twenty years, which represents 10% of the global population. Nevertheless, the risk of amputation remains high, and some patients remain undiagnosed until it is too late to prevent LEA (18). In a cohort of patients with diabetes, 18% had a cardiovascular disease with PAD being most prevalent (19). Among patients diagnosed with both diabetes and PAD, the risk of amputation is 1.5 times higher than in patients diagnosed with PAD alone and five times higher than in

patients only diagnosed with diabetes (20). To ensure early identification of patients at risk of amputation, we need more knowledge about the progression of LEA-related diseases. This knowledge is reflected in the historic use of medication and the need for healthcare services across all groups of patients with LEAs. The aim of this study was to examine the progression of LEA-related diseases. We examined the use of medication and the number of contacts with healthcare services during the 14 years leading up to LEAs, in an unselected population of all Danish patients that underwent LEAs. With these data, we also studied the associations between LEA-related diseases and the one-year prognosis after the LEA

Methods

Setting

The Danish healthcare system is tax-funded and offers free and equal access to medical care. All citizens have a general practitioner (GP) who provides referrals to specialists and hospital treatments. The GPs are responsible for their patients' medical treatment. Prescribed medications and other healthcare services, such as a physiotherapy etc., are partly tax-funded, with a differential out-of-pocket fee.

Study design and data sources

We included data from the following five nationwide registries: (1) The National Patient Registry (NPR) which contains information on hospitalisations, including visits to outpatient clinics and emergency rooms (21), surgical procedures, coded according to the Nordic Classification of Surgical Procedures (NCSP), and diagnoses coded according to the International Classification of Diseases (ICD-10) ; (2) The National Prescription Registry contains information on prescribed medications picked up at the pharmacy (22). Medications are coded according to the global Anatomical Therapeutic Chemical (ATC) classification system; (3) The Danish National Health Service Registry for Primary Care (NHSR) contains information on all contacts with GPs, including out-of–hours care from GPs and practising medical specialists(23); (4) The Danish Civil Registration System (CRS) contains information on gender, date of birth, vital status, spouses and residents, (24); (5) The Attainment Registry contains data on education level. All Danish citizens are registered with a unique personal identification number (CPR number), which allows linkage with all nationwide registries at an individual level. All data were provided by Statistics Denmark (http://www.danmarksstatistik.dk/en).

Study cohort

We included patients who had undergone at least one of the following surgical procedures, performed between the 1st of January 2010 and 31st of December 2011: hip-exarticulation, trans-femoral amputation (i.e., Above-knee amputation [BKA]); knee disarticulation or trans-tibial amputation (i.e., below-the-knee amputation [BKA]); ankle or foot amputation; or toe amputation. See supplementary materials for detailed information. To eliminate trauma-related amputations, we excluded patients with a trauma diagnosis recorded at any time prior to the amputation. We also excluded foreign patients without a CPR number and patients below 18 years of age. Furthermore, to ensure homogeneity within the groups, we defined an index amputation as the first surgical amputation performed as an AKA, BKA, ankle-, foot- or toe amputation in 2010 and 2011.

Categorisation of amputation procedures

For patients who received more than one amputation procedure on the same day, the most severe procedure was identified and was used for analysis. The severity of different types of amputations (based on surgical codes) was ranked from the most severe procedure as hip-exarticulation and transfemoral amputation to the least severe as a toe amputation procedure. Detailed description is present in the supplementary material. When patients had both a left- and right-side amputation code on the same day, the procedure was categorised as a bilateral amputation.

The definition of the index amputation was based on the surgical amputation procedures and was divided into the following four groups: AKA, BKA, foot/ankle amputation, and toe amputation. AKA and BKA were classified as major amputations, and foot/ankle or toe amputations were classified as minor amputations.

Demographics, comorbidities, medications, and contacts with healthcare services

For each patient, we retrieved cumulative registry information on the education level, living conditions, socioeconomic status, place of residence, diagnoses, prescribed medications, contacts with healthcare services, re-amputations, and death, which had been recorded between 01.01.1997 and 31.12.2012. The Elixhauser Comorbidity Index was used to identify the progression of comorbidities over the 14 years prior to amputation. The Index included 31 pre-defined comorbidities; however, in this study, we combined the pre-defined codes for uncomplicated and complicated diabetes and hypertension (34). To describe comorbidity, the Elixhauser Comorbidity Index was supplemented with ICD-10 codes for atherosclerosis. Further subgroups were created, including atherosclerosis in the lower extremities, diabetic neuropathy, retinopathy, nephropathy foot ulcer, other ulcers-not related to diabetes, stroke, emboli, bone cancer, and arthrosis, see supplementary material. The severity of the comorbidity identified at the time of the index amputation was evaluated with the Charlson Comorbidity index (25). We divided the patients into three groups, according to the Charlson Comorbidity index: 0-1, 2, and 3+, where a higher score predicted a higher risk of mortality. The prescribed medications were defined as medications that were picked up from the pharmacy at least once each year. The prescribed medications were grouped according to ACT codes (see Table 2). The coding and the classifications of drugs were defined by the authors and validated by consensus agreement among three pharmacists who did not participate in the study. See supplementary material.

The NPR registry contains only information on diagnoses recorded during hospitalisation, and not by GPs. Therefore, central diseases were defined by combining the prevalence of the medication (ACT- codes) collected from the pharmacy with the registered diagnosis (ICD-10 codes) from hospitals: diabetes^{comb}, atherosclerosis^{comb}, cardiovascular diseases^{comb} and hypertension^{comb} (see supplementary material). A visit to a GP was defined as a show-up at the GP clinic and visits to outpatient clinics included only clinics at the hospitals.

Ethical approval

This register-based study included only anonymous data from national registries and had no patient contact. The scientific board of Statistics Denmark and “Statens Serum Institut” approved the study (project no 704122).

Statistics

Descriptive data, comorbidities, and the use of medication for each of the amputation groups (AKA, BKA, and minor amputation) were expressed as frequencies with percentages, for categorical data, or as median and intraquartile range (IQR = 25th to 75th percentile) for continuous data. A comparison between major (AKA and BKA) and minor amputations was made with a χ^2 test, for categorical data, and a Kruskal Wallis test for continuous data. Diagnoses and relevant medications were compared for atherosclerosis, diabetes, and hypertension. The prevalence of diagnoses and use of medications over time are depicted as graphs of the proportions of patients with a given disease, and the proportion that used a given medication, respectively. The difference in prevalence over time is expressed as percent point (pp). The data analysis was performed with SAS 9.4, and the cumulative incidence plots were constructed with R 3.2.2. Graphs of the progression over time were created with GraphPad Prism 6.07, and the flowchart was created in Power Point 2010. P-values less than 5% were considered significant.

Results

A total of 3375 patients underwent an LEA in Denmark during 2010 and 2011. Of these, 4% required LEAs due to trauma, and were excluded from the cohort (Figure 1). Additionally, 352 patients (11%) were excluded, due to a previous amputation on the same or opposite leg, at the same or a higher level. A total of 2883 patients fulfilled the criteria for undergoing an index amputation during 2010 and 2011. Major amputations were performed in 1782 patients (62%), and minor amputations were performed in 1101 patients (38%). Patient characteristics are presented in Table 1. Among patients with major amputations, 1562 (88%) had not received previous amputations. Among the 266 patients with previous amputations (on a lower level), 101 patients (38%) were bilaterally amputated.

Comorbidities and medical treatment in the year of amputation

Patient diagnoses and current medications that were recorded at the time of the index amputation are presented in Table 2 and 3. Both diabetes and atherosclerosis were diagnosed in 32% of patients (577/1782) with major amputations and 35% of patients (382/1101) with minor amputations. Furthermore, among patients diagnosed with atherosclerosis, 42% (851/2017) had not received cholesterol-lowering drugs at the time of amputation. The absence of cholesterol-lowering treatment was observed significantly more among patients with major amputations than among those with minor amputations, (46% (650/1428) vs 34% (201/589); p< 000.1). Among the 1407 patients diagnosed with diabetes, 225 patients (16%) did not at any time receive insulin or blood glucose-lowering drugs preceding the amputation. The absence of antidiabetic treatment prior to the amputation was observed significantly more often among patients with major amputations than among patients with minor amputations (19% (134/697) vs 13% (91/710), p <.001).

Disease progression and medications during the 14 years prior to amputation

Figure 2 shows the gradual increases in the proportion of patients with the most common diagnoses (atherosclerosis, diabetes, and hypertension) recorded during hospitalisations and the medications used (including antithrombotic agents, cholesterol-lowering treatments, antidiabetic drugs, and antihypertensive therapies) during the 14 years prior to the amputation. Among patients undergoing major amputations, the prevalence of atherosclerosis increased from 2% to 20% over the first 13 years, and a 58 pp increase was observed during the last year preceding the amputation. During the 14 years, the use of cholesterol-lowering drugs increased from 3% to 50%. There was a 28 pp difference between patients diagnosed with atherosclerosis who received cholesterol-lowering treatment or not prior to the amputation. Furthermore, the use of antithrombotic drugs increased from 15% to 65% during the first 13 years, and the use further increased by 6 percent point in the last year (Figure 2a). Among patients with minor amputations, the prevalence of diabetes increased from 8% to 40%, and antidiabetic treatments increased from 29% to 55%. During the last year, the prevalence of diabetes increased by 21 percent point, and the gap between treatment and diagnosis was only 3 percent point prior to minor amputation (Figure 2b).

Antihypertensive treatments increased from 23% to 60% during the first 13 years, and then dropped slightly, by 4 percent point, in the last year prior to a major amputation. Similarly, antihypertensive treatments increased from 20% to 64% over the 14 years prior to minor amputations (Figure 2c). The use of beta blocking agents increased from 10% to 41% prior to major amputations and from 8% to 38% prior to minor amputations.

The estimated disease progressions, calculated as the combination of the diagnosis prevalence and the medication prevalence, are presented in Figure 3. The progression of diseases prior to a major amputation increased as follows: atherosclerosis^{comb} increased from 5% to 53% during the 14 years, with a 16 percent point increase in the last five years

preceding amputation; hypertension[comb] increased from 23% to 63%; cardiovascular diseases[comb] increased from 22% to 70%; and diabetes[comb] increased from 17% to 35%. The use of opioids increased from 10% to 45%, with an 18 percent point increase the last five years prior to amputation. Further, 32% received prescribed opioids three years prior to major amputation (Figure 3a). Among patients with minor amputations, the prevalence of atherosclerosis[comb] increased from 3% to 51% during the 14 years; cardiovascular diseases[comb] increased from 16% to 63%; hypertension[comb] increased from 20% to 66%; and diabetes increased from 29% to 57%. The use of opioids increased from 9% to 34%, with a 12 percent point increase in the last five years (Figure 3b).

Contacts made to hospitals and GPs during the 14 years prior to amputation

Patients' visits to the healthcare system (hospitals, outpatient clinics, and GPs) during the 14 years prior to amputation are presented in Figure 4. 98% of the patients contacted healthcare services at least once during the last year prior to amputation. The proportion of patients that contacted their GPs increased from 85% to 97% during the 14 years prior to amputation. The mean number of visits to GPs each year increased from 4.5 to 7.7 visits per year. The proportion of patients that visited outpatient clinics increased from 25% to 76%, and the mean number of visits to outpatient clinics per year increased from 0.4 to 3.2 visits. The number of hospitalisations increased from 17% to 49%. During the last year prior to amputation, 2% of the patients had no contact with GPs or hospitals, 1% had only contacted hospitals, and 18% had only contacted GPs.

Among 851 patients diagnosed with arteriosclerosis without receiving cholesterol-lowering drugs at any time prior to the amputation, 87% had visited their GP, 29% had called out-of-hours care, 47% had been hospitalised, 70% had visited outpatient clinics, and 29% had visited the emergency room during the last year prior to amputation.

Cumulative incidences of death and re-amputation

Figure 5 shows the cumulative incidences of death and re-amputation for first year after LEA. The hazard ratios for death the first year after an AKA (compared to foot/ankle amputation) were 4.41 (95%CI: 3.44-5.66, p<0.001) with no adjustments, 3.39 (95%CI: 2.64-4.37, p<0.001) after adjusting for demographics (sex, age, and living conditions), and 4.0 (95%CI: 3.09-5.19, p<0.001) after also adjusting for co-morbidities (diabetes, arteriosclerosis, hypertension, and use of opioids). The hazard ratios for death the first year after a BKA (compared to foot/ankle amputation) were 2.57 (95%CI: 1.97-3.19, p<0.001) without adjustments, 2.28 (95%CI: 1.75-2.97, p<0.001) after adjusting for demographics, and 2.39 (95%CI: 1.83-3.13, p<0.001) after also adjusting for co-morbidity.

The hazard ratios for re-amputation the first year after an AKA were 4.16 (95%CI: 3.24-5.34, p<0.001) without adjustments, 3.20 (95%CI: 2.49-4.13, p<0.001) after adjusting for demographics, and 3.69 (95%CI: 2.85-4.79, p<0.001) after also adjusting for co-morbidity. The hazard ratios for death the first year after a BKA were 2.64 (95%CI: 2.02-3.43, p<0.001) without adjustments, 2.34 (95%CI: 1.79-3.05, p<0.001) after adjusting for demographics, and 2.4 (95%CI: 1.83-3.14, p<0.001) after also adjusting for co-morbidity.

Discussion

This study showed that the prevalence of atherosclerosis was 70% and the prevalence of diabetes was 49% in an unselected national cohort of patients undergoing LEAs. Of the patients with atherosclerosis, 42% had not received cholesterol-lowering treatments, although 87% of these patients had visited their GP at least once during the last year prior to amputation. Additionally, 16% of the patients with diabetes were diagnosed with diabetes the year of the amputation. The majority of patients (85%) had at least one GP contact per year throughout the 14 years prior to amputation, and 64% were in contact with a hospital outpatient clinic three years prior to amputation. Another important finding was that 88% of patients undergoing major extremity amputations had no previous amputations on a lower level. Moreover, only 6% of patients in this cohort had undergone revascularisation prior to amputation. Nevertheless, one out of three patients received prescribed opioids three years prior to amputation.

Traditionally, LEA has primarily been associated with long-term complications to diabetes. However, the prevalence of cardiovascular diseases has increased in western countries; consequently, the traditional perceptions must be redefined to identify risk factors for LEA. In our unselected national cohort of patients with major amputations, the majority (83%) was diagnosed with atherosclerosis, and a smaller proportion had diabetes (33%). In comparison, patients with minor amputations had a higher prevalence of diabetes (64%) and lower prevalence of atherosclerosis (53%). Similar distributions were also identified by The Global Lower Extremity Amputation Study Group, 2000 (13). Further, we also found a 28 percent point difference between the proportion of patients who received cholesterol-lowering drugs and the proportion of patients diagnosed with atherosclerosis. Also, among patients with diabetes there was a six percent point gap between patients having diabetes and patients receiving anti-diabetic treatment, indicating an unsolved clinical problem in identifying atherosclerosis and diabetes. Indeed, timely treatment might have saved these

patients from a extremity amputation. The lack of recognition of symptoms related to PAD among both patients and health care professionals may be related to a lack of knowledge that inhibited patients to react on symptoms and consult their GP in time (26). However, the increased use of prescribed opioids in the years leading up to the amputation could indicate the presence of PAD, all though we have no information on the indication for the prescription. This study supports the conclusion made by Jones et al. that calls for education programs to focus on prevention and early identification to ensure adequate treatment for preventing LEA (5).

In this study, few patients had a history of minor amputations performed prior to the major index amputation; 89% and 85% of patients with AKA and BKA, respectively, had no history of previous amputation preceding the first-time major amputations. Heyer et al. reported that 92 % of their patients had no previous amputation based on data from health insurance companies (12) and Buckley et al. found that 28% of a selected cohort of patients with diabetes had a history of amputations (16). Further, Currran et al. reported that 61% had a history of either revascularisation or amputation based on data from a surgeon database (3). In this study, only 6% of the patients had received revascularisations (angioplasty or bypass) prior to the index amputation. These results were surprising as revascularisation surgery is still considered one of the central treatment strategies for critical ischaemia in lower extremities (27,28). Similarly, Moxey et al. found a 9% prevalence of revascularisation in an unselected, nationwide cohort (29). However, Ahmad et al. found a 30% prevalence of revascularisation in an unselected population cohort in England (11). Ahmad et al. also demonstrated demographic variations in the prevalence of amputations and revascularisations, which were associated with social inequalities and the presence of chronic diseases in some geographical regions. The finding that one third of patients received intensive pain treatment already three years prior to major amputation indicate symptoms of ischaemia, which appear several years prior to amputation. Thus, it is essential that leg pain should be recognised as a symptom of PAD to ensure that patients are referred

to specialists (30). In Denmark, the ankle and toe blood pressures are measured to calculate the Ankle-Brachial index (ABI) (31), a non-invasive diagnostic test for PAD (32). This procedure is mainly performed in hospitals, and rarely by the GP. The majority of patients' maintained regular and increasing contact with their GPs, thus, early identification might be feasible, because patients do seek medical advice in the years prior to the amputation. Furthermore, our results showed that 63% of patients were also in regular contact with outpatient clinics at hospitals already three years before the amputation, and they increasingly (from 32% to 49%) underwent hospitalisation during the last years preceding amputation. Buckley et al. followed patients with diabetes for seven years prior to LEA, and concluded a need for early referral to specialists to reduce risk of LEA (16). Our study found that the majority (76%) of patients visited the out-patient clinic and as such is accessible for early identification. It has been suggested that PAD screening could be performed with non-invasive methods, like the ABI (33); . Other studies have indicated that routine screening could promote preventive treatment, and that a screening strategy could cost-effectively prevent the progression of PAD and cardiovascular events (34,35). Alternatively, Brand (36) and Boulton et al. (37) have suggested that a simple clinical examination of a patient's feet could indicate a need for further test to identify PAD. Thus, treatment could be initiated (including specialist referrals) to prevent ulcers due to ischaemia, and thus, prevent LEA.

The present study confirmed that the risk of re-amputation increased after minor amputations, and that the risk of death was highest among patients who required AKAs. In contrast, neither demographics nor comorbidities could explain the low chance of survival. Thus, other factors must affect the outcome after LEA, such as the general health status and the nutritional status of a patient. In addition, factors related to the perioperative treatment, like the delay to surgery, could have a negative impact on the outcome (38). Similar results

were reported by Jones et al., Hoffstad et al., and Wiessman et al., who called for more comprehensive, multidisciplinary efforts (5,7,10).

The strength of this study was the use of an unselected, nationwide cohort based on the national registry, which maintained information recorded over a period of 14 years prior to the amputation. Furthermore, we could crosslink data in various registries at an individual level, which made it possible to follow patients over time. The main limitation was the lack of a control group. An age-, sex-, and geographically-matched control group could allow differentiation between disease progression due to aging and disease progression that leads to amputation. Furthermore, this type of comparison could also reveal inequalities in healthcare services, as has been shown in other countries (11). An inherent limitation was that the data did not allow an estimation of patient compliance with the prescribed medication. Further, it was not possible to access the diagnosis recorded by the GP, as these data are not included in the national registry nor the indication for the prescribed medication as this has just recently been included in the registry.

Conclusion

Atherosclerosis is the primary comorbidity followed by hypertension and diabetes in this unselected cohort of patients undergoing major extremity amputation. In this study, one third of patients with LEA were living with undiagnosed or untreated atherosclerosis and one out of six were living with undiagnosed diabetes despite a regular contact with their GPs and outpatient clinics for several years prior to the amputation. For the majority of patients undergoing major LEAs, the amputation was a first-time amputation. Additionally, only a small number of patients underwent extremity-saving procedures, although one in three had received opioid prescriptions several years before the amputation. The overall findings of this study suggest that the need of opioids, combined with the presence of hypertension, diabetes, or another cardiovascular disease, could be an indication of PAD which is highly

associated with lower extremity amputation. Further, clinicians are encouraged to initiate medical treatment supplemented with a careful inspection of the patient´s feet as this non-invasive examination may detect an early indication of low circulation.

Acknowledgements

We acknowledge the contribution from Research Services, Statistics Denmark for management and access to registry data and thank Jørn K Petersen for his assistance. We especially thank Nasrin Faqir, for her contribution to data management and analysis.

Competing interest

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests

Funding

This study was funded by The Novo Nordic Foundation grant number NNF12OC0002017, and Copenhagen University Hospital, Hvidovre Research Foundation. None of the sponsors were involved in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Consent for publication

Not applicable

Data sharing statement

The datasets supporting the conclusions of this article are available in the Statistics Denmark, http://www.dst.dk/. Statistics Denmark managed and providedthe secured access In according to Danish regulations, data are available by applying Statistics Denmark.

Author contributors

SJ and JP describe the idea behind the study. PSJ and OA applied for funding to the study. PSJ, JP, KKM, IP and OA signed the study. PSJ and JP applied for data at Statistics Denmark. PSJ and JP provided the statistical expertise. IP, KKM and OA provided the clinical and medical expertise. PSJ and JP performed the data management and analysis. All authors helped interpret the data. The accuracy of data and analysis was reviewing by all authors who can take responsibility for the integrity of the data and the accuracy of the data

443 analysis. PSJ drafted the manuscript. All authors reviewed and critically revised the

444 manuscript for intellectual content and approved the final version of the manuscript.

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Table 1. Characteristics of patients with lower extremity amputations in 2010-2011 in Denmark

	Total N (%)	Major amputation		Minor amputation N (%)
		Above-Knee N (%)	Below-Knee N (%)	
n	n=2883	n = 1024	n=758	n=1101
Gender				
Male	1811 (63)	544 (53)	489 (65)	778 (71)
Age				
Men, median (IQR)	69 (61;79)	74 (66;82)	70 (60;78)	66 (58;76)
Women, median (IQR)	78 (68;86)	81 (72;87)	78 (68;85)	72 (63;82)
Social status[1]				
Married[2]	1165 (40)	378 (37)	307 (41)	480 (44)
Divorced	937 (32)	293 (29)	247 (33)	397 (36)
Widow	767 (27)	352 (34)	200 (26)	217 (20)
Economic status				
Working	257 (9)	24 (2)	62 (8)	171 (16)
Retired	2055 (71)	845 (83)	534 (71)	676 (61)
Social welfare	571 (20)	155 (15)	162 (21)	254 (23)
Living arrangement				
Living alone	1514 (53)	595 (58)	402 (53)	517 (47)
Living in rural areas	1705 (59)	634 (62)	431 (57)	640 (58)
Education				
< 9 year of school	2549 (88)	896 (88)	662 (87)	9991 (90)
Charlson Index				
0-1	546 (19)	196 (19)	133 (17)	217 (20)
2	456 (16)	217 (21)	105 (14)	134 (12)
3	1881 (65)	611 (60)	520 (69)	750 (68)
Multi-morbidities and Polypharmacy				
Co-morbidities[3], median (IQR)	7 (5;9)	6 (5;9)	7 (5;10)	7 (4;9)
Drugs[4], median (IQR)	7 (5;9)	7 (5;9)	7 (5;9)	6 (4;8)
Peripheral vascular procedure				
Angioplasty	89 (3)	7 (1)	4 (1)	78 (7)
Bypass graft	97 (3)	5 (0,5)	4 (1)	88 (8)
Surgery history				
Previous amputation	266 (9)	113 (11)	107 (14)	46 (4)
< 3 amputations	203 (7)	84 (8)	76 (14)	43 (4)
≥ 3 amputations	63 (2)	29 (3)	31 (4)	3 (-)

Values represent the number of patients (%), unless indicated otherwise. [1]Missing n=12. [2]Married or residing with a partner. [3]All ICD10 diagnoses. [4]ACTcodes for main groups

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Table 2. Prevalence of comorbidity among patients with lower extremity amputations in 2010-2011 in Denmark

	Major amputations			Minor amputations	
	Total, N (%)	Above Knee n (%)	Below Knee n (%)	Total, N (%)	P value*
	N=1782	N=1024	N=758	N=1101	
Peripheral Vascular Disorders	1481 (83)	873 (85)	608 (80)	625 (57)	<.0001
Atherosclerosis[1]	1428 (80)	844 (82)	584 (77)	589 (54)	<.0001
Hypertension[2]	902 (51)	577 (56)	441 (58)	599 (54)	.18
Diabetes[2]	697 (39)	331 (32)	366 (48)	710 (64)	<.0001
Diabetic foot ulcer[3]	505 (18)	224 (22)	281 (37)	522 (47)	<.0001
Neuropathy[3]	174 (6)	69 (7)	105 (14)	230 (21)	<.0001
Retinopathy[3]	112 (6)	37 (4)	75 (10)	141 (13)	<.0001
Nephropathy[3]	85 (5)	22 (2)	63 (8)	82 (7)	.0028
Cardiac ischaemia[3]	597 (34)	348 (34)	249 (33)	329 (30)	.04
Cardiac Arrhythmia	536 (30)	319 (31)	215 (28)	232 (21)	<.0001
Cerebrovascular disease[4]	540 (30)	317 (31)	223 (29)	195 (18)	<.0001
Congestive Heart Failure	401 (23)	228 (22)	173 (23)	191 (17)	.0009
Stroke[3]	401 (23)	234 (23)	167 (22)	144 (13)	<.0001
Arthrosis[3]	320 (18)	202 (20)	118 (16)	195 (18)	.86
Chronic Pulmonary Diseases	356 (20)	227 (22)	129 (17)	129 (12)	<.0001
Fluid & electrolyte disorders	330 (19)	211 (21)	119 (16)	123 (11)	<.0001
Emboli[3]	359 (20)	231 (23)	128 (17)	88 (8)	<.0001
Renal Failure	252 (14)	129 (13)	123 (16)	133 (12)	.11
Tumor without Metastasis	243 (14)	143 (14)	100 (13)	107 (10)	.0018
Alcohol addiction	227 (13)	121 (12)	106 (14)	122 (11)	.18
Obesity	130 (7)	60 (6)	70 (9)	127 (12)	.0001
Rheumatoid Arthritis	139 (8)	77 (8)	62 (8)	90 (8)	.71
Depression	124 (7)	77 (8)	47 (6)	58 (5)	.069
Dementia[5]	110 (6)	69 (7)	43 (6)	37 (3)	.0006
Liver disease	79 (4)	40 (4)	39 (5)	51 (5)	.80
Metastatic Cancer	50 (3)	36 (3)	14 (2)	9 (1)	.0002
Weight loss	43 (2)	30 (3)	13 (2)	12 (1)	.0155
Bone Cancer[3]	24 (1)	14 (1)	10 (1)	2 (-)	.0013

*P<0.05, major vs. minor amputation. Comorbidity, defined according to Elixhauser Comorbidity index;[1] includes only ICD10- I170; [2] includes uncomplicated and complicated conditions; [3] not included in the Elixhauser Comorbidity index; [4]included from the Charlson Comorbidity index

Table 3. Prevalence of prescribed medications used by patients with lower extremity amputations in 2010-2011 in Denmark

	Major amputations			Minor amputations	
	Total, N (%)	Above Knee n (%)	Below Knee n (%)	Total, N (%)	P value*
	N=1782	N=1024	N=758	N=1101	
Opioids	1484 (83)	876 (86)	608 (80)	684 (62)	<.0001
Antithrombotic drugs	1262 (71)	738 (72)	524 (69)	711 (65)	.0005
Acetaminophen	1333 (75)	802 (78)	531 (70)	621 (56)	<.0001
Antihypertensives	1000 (56)	577 (56)	423 (56)	715 (65)	<.0001
Cholesterol-lowering drugs	886 (50)	481 (47)	405 (53)	627 (57)	.0002
Neuropathic pain relievers	919 (52)	517 (50)	402 (53)	330 (30)	<.0001
Antidepressants	864 (48)	501 (49)	363 (48)	365 (33)	<.0001
Antidiabetic therapy	588 (33)	268 (26)	320 (42)	638 (58)	<.0001
Beta blockers	760 (43)	440 (43)	320 (42)	439 (40)	0.14
NSAID	451 (25)	264 (26)	187 (25)	312 (28)	0.07
Drugs for airway disease	337 (19)	199 (19)	138 (18)	146 (14)	<.0001
Alcohol addiction	341 (19)	198 (20)	143 (19)	122 (11)	<.0001
Smoking cessation	259 (15)	155 (15)	104 (14)	132 (12)	.053
Cortisol	246 (14)	156 (15)	90 (12)	120 (11)	.023

*P<0.05, major vs. minor amputation

Figures titles and legends

Figure 1

Title: Figure 1. Flowchart shows study selection of patients with lower extremity amputations between 01.01.2010 -31.12.2011 in Denmark

Legends: (1) Excluded due to previous amputation define as amputation on the same level or bilateral amputation on a higher level than the index amputation in 2010-11; (2) include hip-exarticulation; (3) include knee disarticulation.

Figure 2

Title: Figure 2. The prevalence of comorbidities and prescribed medications during the 14 years preceding major and minor lower extremity amputations.

Figure 3

Title: Figure 3. 14 years of estimated progression of chronic diseases preceding (a) major and (b) minor lower extremity amputations.

Legends: The prevalence of comorbidities, defined by both ICD-10 coding and the use of prescribed medications (ACT code), was estimated each year.

Figure 4

Title: Figure 4. Contacts with the healthcare system during the 14 years preceding lower extremity amputation. Patients are grouped according to (a) major amputations, and (b) minor amputations

Figure 5

Title: Figure 5. One-year cumulative outcomes. The cumulative probabilities of (*left*) re-amputation procedures and (*right*) survival are shown for patients that received major (AKA and BKA) and minor lower extremity amputations

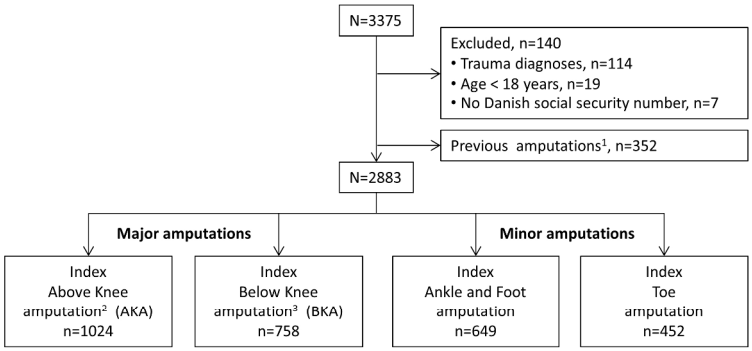


Figure 1. Flowchart shows study selection of patients with lower extremity amputations between 01.01.2010 -31.12.2011 in Denmark

Legends: (1) Excluded due to previous amputation define as amputation on the same level or bilateral amputation on a higher level than the index amputation in 2010-11; (2) include hip-exarticulation; (3) include knee disarticulation.

254x190mm (300 x 300 DPI)

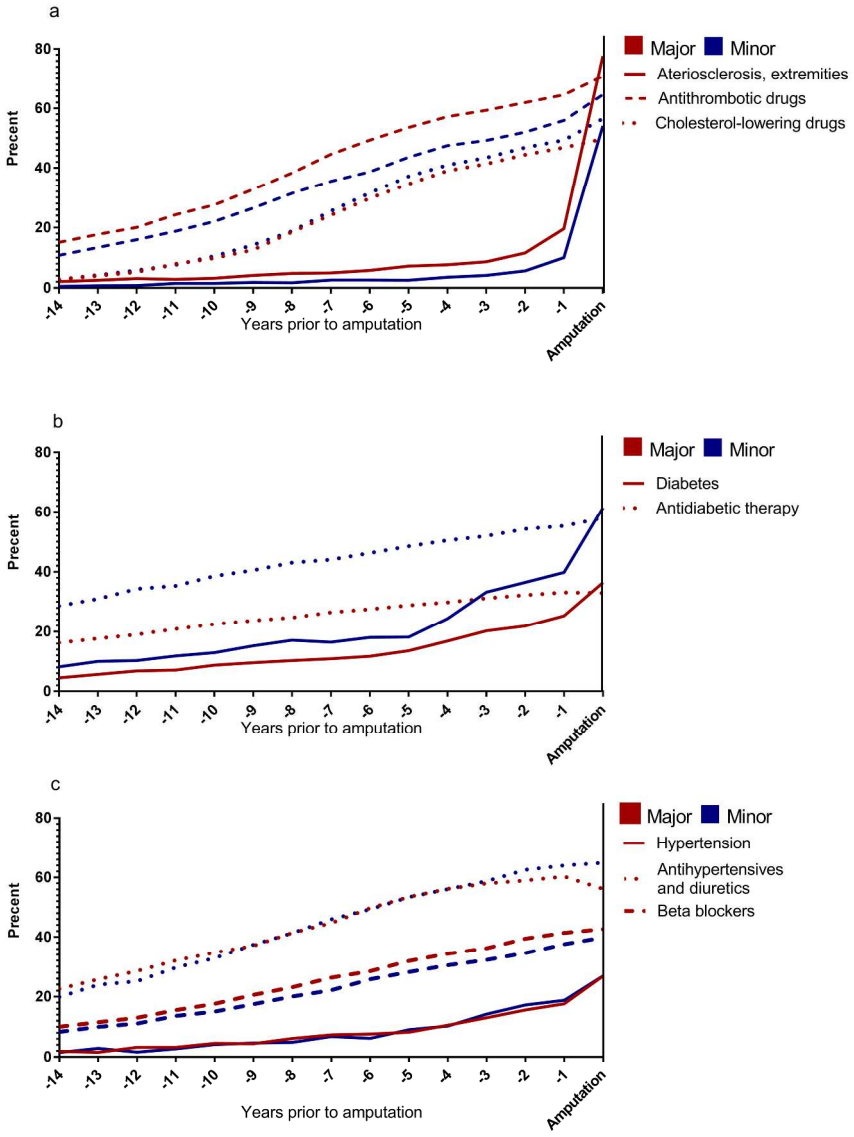
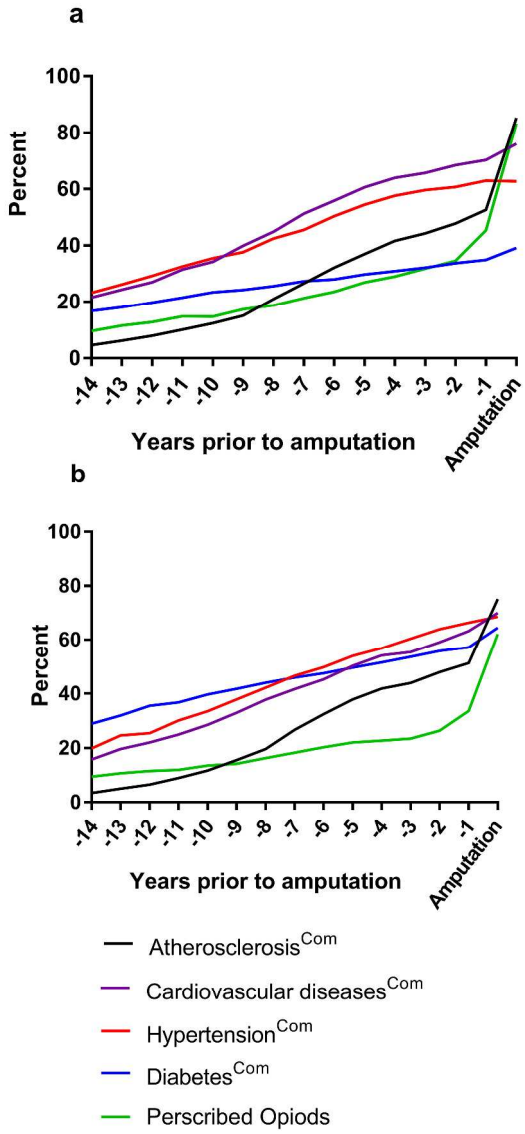


Figure 2. The prevalence of comorbidities and prescribed medications during the 14 years preceding major and minor lower extremity amputations.

242x299mm (300 x 300 DPI)



itle ‼ ┼ Figure 3. 14 years of estimated progression of chronic diseases preceding (a) major and (b) ‼ ┼ minor lower extremity amputations. ‼ ┼ Legends‼ ┼ The prevalence of comorbidities, defined by both ICD-10 coding and the use of prescribed medications (ACT code), was estimated each year. ‼ ┼

293x570mm (300 x 300 DPI)

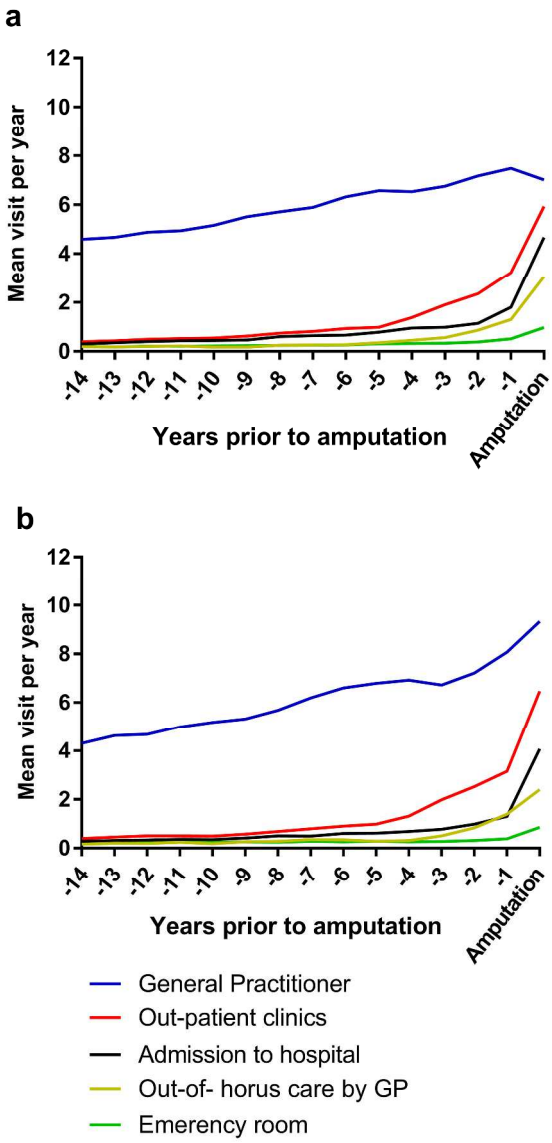
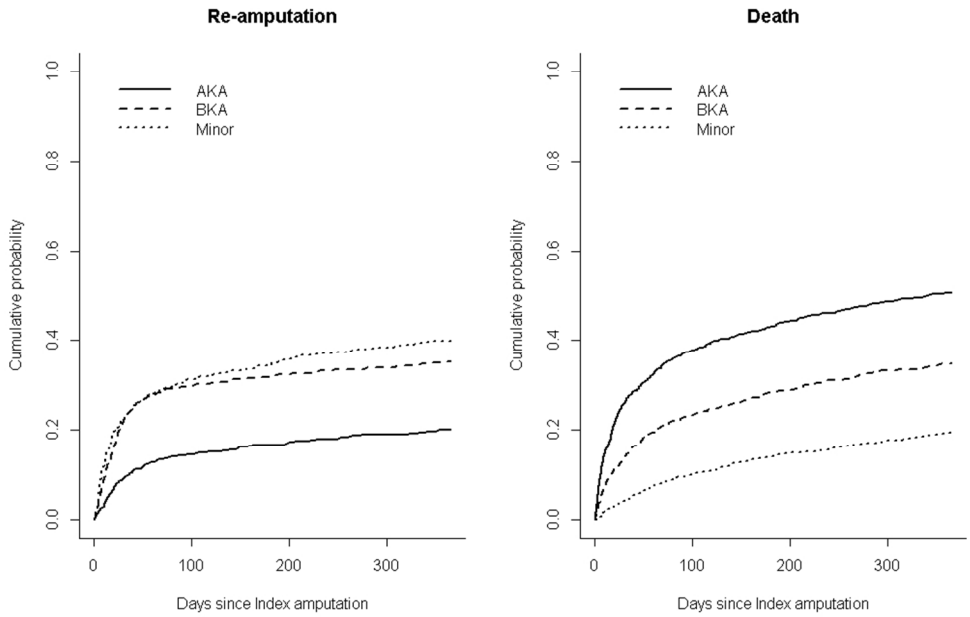


Figure 4. Contacts with the healthcare system during the 14 years preceding lower extremity amputation. Patients are grouped according to (a) major amputations, and (b) minor amputations

219x402mm (300 x 300 DPI)



Title‼ ┼ Figure 5. One-year cumulative outcomes. The cumulative probabilities of (left) re-amputation procedures and (right) survival are shown for patients that received major (AKA and BKA) and minor lower extremity amputations

365x239mm (72 x 72 DPI)

Progression of disease preceding lower extremity amputation: A longitudinal registry study of diagnoses, use of medication and healthcare services 14 years prior to amputation

Supplementary material

SKS codes for surgical procedure, identification of index amputation

Above Knee Amputation (AKA)

Hip-exarticulation	(KNFQ09)
Trans-Femoral amputation	(KNFQ19, KNFQ99)

Below Knee Amputation (BKA)

Knee disarticulation	(KNGQ09)
Trans-Tibial amputation	(KNGQ19, KNGQ99)
Ankle or foot amputation	(KNHQ00-08)
Toe amputation	(KNHQ10-18, KNHQ 90-99)

Rank of amputation procedure

1. Hip-exarticulation	(KNFQ09)
2. Trans-Femoral amputation	(KNFQ19, KNFQ99)
3. Knee disarticulation	(KNGQ09)
4. Trans-Tibial amputation	(KNGQ19,KNGQ99)
5. Ankle and foot amputation	(KNHQ10-18, KNHQ 90-99)
6. Revision of stump or related amputation procedure after Hip-exarticulation or Trans-Femoral amputation	(KNFQ29, KNFQ39, KNFQ49)
7. Revision of stump or related procedure after Knee disarticulation or Trans-Tibial amputation	(KNGQ29, KNGQ39, KNGQ49)
8. Toe amputation	(KNHQ00-08)
9. Stump revision of foot, ankle or toe amputation	(KNHQ20-28)

Progression of disease preceding lower extremity amputation: A longitudinal registry study of diagnoses, use of medication and healthcare services 14 years prior to amputation

ICD10 code for diagnosis

Atherosclerosis	DI70
Atherosclerosis, extremities	D1702
Diabetes	
Neuropathy	DE104, DE114, DE124, DE134, DE144
Retinopathy	DE103, DE113, DE123, DE133, DE143
Nephropathy	DE102, DE122, DE132, DE142
Foot ulcer	DE105, DE115, DE125, DE135, DE145
Ulcer	Dl97, DL88, Dl89, DL984, DS91, DR02, DL02
Apoplexia	DI60, DI61, DI62, DI63, DI64
Emboli	DI80, DI81, DI82, DI74
Bone cancer	DC40, DC41, DC49
Arthrosis	DM15, DM16,DM17, DM18, DM19

ACT codes for medication

Antidiabetic therapy	
Insulins	A10A
Blood Glucose lowering drugs	A10B
Antithrombotic drugs	B01A
Drugs for hypertension	
Antihypertensives	C02DB, C02CA, C08, C09
Diuretics, Thiazides, plan	C03AA - Eller hele gruppen C03 Diuretics ?
Beta blockers	C07
Cholesterol-lowering drugs	C10AA, C10AB, C10AD, C10AX, C10B
Corticosteroids for systemic use	H02A
Obstructive airway disease	R03
Opioids	N02A

Progression of disease preceding lower extremity amputation: A longitudinal registry study of diagnoses, use of medication and healthcare services 14 years prior to amputation

Codeine	R05DA04
Acetaminophen	N02B
NSAID	M01A
Neuropathic pain relievers	
Antiepileptics drugs	N03AX
Antidepressants	N06AA, N06AX
Drugs for alcohol addiction	N07BB, N03AA, N05BA
Drugs for smoking cessation	N07BA, N06AX,

Codes used to estimate the progression of diseases over 14 years prior to amputation by combining diagnosis and prescribed medication

Atherosclerosis[Com]

Arteriosclerosis	ICD code DI70
Cholesterol-lowering drugs	ACT code C10AA, C10AB, C10AD, C10AX, C10B

Diabetes[Com]

Diabetes	ICD code DE10, DE11, DE12, DE13, DE14
Antidiabetic therapy	ACT code A10A, A10B

Cardiovascular diseases[Com]

Cardiac ischemia	ICD code DI20, DI21, DI22, DI23, DI24, DI25,
Congestive heart failure, cardiac arrhythmia,	Elx_GRP_1, ELX_GRP_2
Beta blockers, Antithrombotic drugs	ACT code C07, B01A

Hypertension[Com]

Hypertension	ICD code DI10, DI11, DI12, DI13, DI,15
Drugs for hypertension	ACT code C02DB, C02CA, C03AA, C08, C09

Prescribed opioids

ACT code, opioids	ACT code N02A, R05DA04

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page, p 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6,7
Methods			
Study design	4	Present key elements of study design early in the paper	Page 8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 8, 9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 10
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Page 9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 10,11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 11
		(*b*) Describe any methods used to examine subgroups and interactions	Page 11
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 12, (Figure 1)
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 12, (Table1)
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 13,14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 15
		(*b*) Report category boundaries when continuous variables were categorized	Tabel 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 15,16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 16
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Progression of disease preceding lower extremity amputation in Denmark: A longitudinal registry study of diagnoses, use of medication and healthcare services 14 years prior to amputation

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016030.R1
Article Type:	Research
Date Submitted by the Author:	09-Jun-2017
Complete List of Authors:	Jensen, Pia; Copenhagen University Hospital, Hvidovre, Optimed, Clinical Research centre Petersen, Janne; Copenhagen University Hospital, Hvidovre, Clinical Research Centre (056); Department of Public Health Section of Biostatistics, University of Copenhagen, Denmark Kirketerp-Møller, Klaus; University Hospital of Copenhagen, Bispebjerg, Copenhagen Wound Healing Centre Poulsen, Ingrid; Traumatic Brain Injury Unit, Rigshospitalet, Copenhagen, Denmark , Clinic of Neurorehabilitation Andersen, Ove; Copenhagen University Hospital, Hvidovre, Denmark, Clinical Research Centre
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Diabetes and endocrinology, Epidemiology, Cardiovascular medicine
Keywords:	Lower Extremity amputation, Atherosclerosis, Diabetes, Health care service

Title

Progression of disease preceding lower extremity amputation in Denmark: A longitudinal registry study of diagnoses, use of medication and healthcare services 14 years prior to amputation

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Word count: 3980

Abstract

Objectives: Patients with non-traumatic lower extremity amputation are characterised by high age, multi-morbidity and polypharmacy and long-term complications of atherosclerosis and diabetes. To ensure early identification of patients at risk of amputation, we need to gain knowledge about the progression of diseases related to lower extremity amputations during the years preceding the amputation.

Design: A retrospective population-based national registry study.

Setting: The study includes data on demographics, diagnoses, surgery, medications, and healthcare services from five national registries. Data were retrieved from 14 years before until 1 year after the amputation. Descriptive statistics were used to describe the progression of diseases and use of medication and healthcare services.

Participants: An unselected cohort of patients (≥50 yrs; n=2883) subjected to a primary non-traumatic lower extremity amputation in 2010 or 2011 in Denmark.

Results: The prevalence of atherosclerosis, hypertension and diabetes was 70%, 53% and 49%, respectively. Among of patients with atherosclerosis, 42 % had not received cholesterol-lowering treatment even though 87% had visited their general practitioner within the last year prior to amputation. Further, 16% were diagnosed with diabetes at the time of the amputation. The prevalence of cardiovascular diseases increased from 22% to 70%, atherosclerosis from 5% to 53%, and diabetes from 17% to 35% over the 14 years preceding major amputation. Of all patients, 64% had been in contact with the hospital or out-patient clinics within the last three years and 29% received a prescription of opioids three years prior to the amputation.

Conclusion: Among patients with non-traumatic lower extremity amputation, one-third live with undiagnosed and untreated atherosclerosis and one-sixth suffer from undiagnosed diabetes despite continuous contacts to general practitioner and the hospital. This study

emphasises a need for enhanced focus, among both hospital clinicians and general practitioners, on the early identification of atherosclerosis and diabetes.

Keywords Lower extremity amputation, Atherosclerosis, Diabetes, Healthcare services

Strengths and limitations of the study

- The strengths of this national registry study were the inclusion of data describing diagnoses and use of medication and healthcare services during the last 14 years preceding non-traumatic LEA performed in Denmark.

- The main limitation was the lack of a control group. An age-, sex-, and geographically-matched control group would have allowed differentiation between disease progression due to aging and disease progression leading to amputation. An inherent limitation was that the data did not allow an estimation of patient compliance with the prescribed medication.

Abbreviations

LEA: lower extremities amputation

Major LEA: Lower extremity amputation performed above the ankle level

Minor LEA: Lower extremity amputation performed below the ankle level

AKA: Above knee amputation

BKA: Below knee amputation

PAD: Peripheral artery disease

GP: General practitioner

Introduction

Lower extremity amputation (LEA) is a severe event associated with loss of mobility, pain, decreased quality of life, major disfigurement, and increased risk of re-amputation and hospitalisation (1–3). Even though the worldwide incidence of LEA has declined over the last two decades, significant variations persist; from 5.8 to 31 per 10^5 individuals in different populations (4). The reported one-year mortality rate was 12% to 58% (5–8), with the highest mortality rate (45% -58%) associated with above-the-knee amputations (AKA) (9,10). Age and the severity of comorbidities are the most prominent prognostic factors for mortality after LEA (6,7).

The most prevalent comorbidities in patients with LEA are atherosclerosis primary as periphery vascular disease (PAD) and diabetes (4,11–13).Studies have reported the prevalence's of diabetes to be between 52%- 64% (3,5,14) and approximately 80 % of the patients with LEA are either diagnosed with diabetes or PAD (12). In a cohort of patients with diabetes, 18% had a cardiovascular disease with PAD being most prevalent (15). Among patients diagnosed with both diabetes and PAD, the risk of amputation is 1.5 times higher than in patients diagnosed with PAD alone and five times higher than in patients only diagnosed with diabetes (13).The global prevalence of diabetes and PAD among patients with LEA varies among populations due to ethnicity and socioeconomic e.g. (4,16). Currently, the global prevalence of diabetes is estimated to 9% of which 90% is characterised as type 2 diabetes (17) and is expected to continue to increase over the next twenty years to 10%. During the last decade, the global prevalence of PAD has increased by 23%, with the highest increase among low-income countries (18). The risk factors for PAD are age, smoking, diabetes, hypertension, dyslipidaemia, and obesity (19). The NICE guidelines for lower limb peripheral arterial disease state that there is substantial evidence establishing benefits for lowering cholesterol drugs for patients with PAD and the use of limb-saving procedure are also recommended (20). The benefits of cholesterol lowering drugs have shown a significant reduction in the risk of major amputation (21,22).

To our knowledge, only a few studies have previously investigated the progression of diseases and use of health-care services before amputation using historical longitudinal data. One case-control study including data collected seven years before amputation and recommended early referral to a medical specialist to prevent LEA among patients with diabetes (23), all though a population-based study found that repeated visit to the hospital did not lower the risk of amputation among patients with diabetes/PAD (24). Other studies have also shown delayed referral to revascularization to prevent loss of extremity and inadequate treatment of cholesterol-lowing drug (25,26)

Nevertheless, the risk of amputation remains high, and some patients remain undiagnosed until it is too late to prevent LEA (27). The first step to improving the early identification is to acquire more knowledge of the characteristics of patients, variation and progression of diseases and use of health care services prior to amputations. The aim of this study was to explore the progression of LEA-related diseases. We examined the use of medication and the number of contacts with health care services during the 14 years leading up to LEA, among all Danish patients that underwent LEAs in 2010 or 2011. Finally, we studied the associations between LEA-related diseases and the one-year prognosis after the LEA

Methods

Setting

The Danish healthcare system is tax-funded and offers free and equal access to medical care. All citizens have a general practitioner (GP) who provides referrals to specialists and hospital treatments. The GPs are responsible for their patients' medical treatment. Prescribed medications and other healthcare services, such as a physiotherapy, etc., are partly tax-funded, with a differential out-of-pocket fee.

Study design and data sources

We included data from the following five national registries: (1) The National Patient Registry (NPR), which contains information on hospitalisations, including visits to outpatient clinics and emergency rooms (28), surgical procedures, coded according to the Nordic Classification of Surgical Procedures (NCSP), and diagnoses coded according to the International Classification of Diseases (ICD-10); (2) The National Prescription Registry, which contains information on prescribed medications picked up at the pharmacy (29), the data are coded according to the global Anatomical Therapeutic Chemical (ATC) classification system; (3) The Danish National Health Service Registry for Primary Care (NHSR), which contains information on all contacts with GPs, including out-of–hours care from GPs and practising medical specialists (30); (4) The Danish Civil Registration System (CRS), which contains information on gender, date of birth, vital status, spouses and residents (31); and (5) The Attainment Registry, which contains data on education level. All Danish citizens are registered with a unique personal identification number (CPR number), which allows linkage with all national registries at an individual level. Statistics Denmark provided the data (http://www.danmarksstatistik.dk/en).

Study cohort

We included patients with at least one of the following surgical procedures, performed between the 1st of January 2010 and 31st of December 2011: Hip-exarticulation or trans-femoral amputation (i.e., Above-knee amputation [AKA]); knee disarticulation or trans-tibial amputation (i.e., Below-the-knee amputation [BKA]); foot amputation; or toe amputation. See supplementary materials for detailed information. To eliminate trauma-related amputations, we excluded patients with a trauma diagnosis recorded at any time prior to the amputation. We also excluded foreign patients without a CPR number or below 18 years of age. To ensure homogeneity within the groups, we defined an index amputation as the first surgical amputation performed as an AKA, BKA, foot- or toe amputation in 2010 and 2011.

Categorisation of amputation procedures

For patients who received more than one amputation procedure on the same day, the most severe (proximal) procedure was identified for analysis. The severity of different types of amputations (based on surgical codes) was ranked from the most severe procedure as hip-exarticulation and transfemoral amputation to the least severe as a toe amputation procedure. A detailed description is present in the supplementary material. When patients had both a left- and right-side amputation code on the same day, the procedure was categorised as a bilateral amputation. AKA and BKA were classified as major amputations, and foot or toe amputations were classified as minor amputations.

Demographics, comorbidities, medications, and contacts with healthcare services

For each patient, we retrieved cumulative registry information on the education level, living conditions, socioeconomic status, place of residence, diagnoses, prescribed medications, contacts with healthcare services, re-amputations, and death, which had been recorded between 01.01.1997 and 31.12.2012. The Elixhauser Comorbidity Index was used to identify the progression of comorbidities over the 14 years prior to amputation. The Index includes 31 pre-defined comorbidities; however, in this study, we combined the pre-defined codes for

uncomplicated and complicated diabetes and hypertension (32). The Elixhauser Comorbidity Index was supplemented with ICD-10 codes for atherosclerosis, including atherosclerosis in the lower extremities, diabetic neuropathy, retinopathy, nephropathy foot ulcer, other ulcers (not related to diabetes), stroke, emboli, bone cancer, and arthrosis, see supplementary material. The severity of the comorbidity identified at the time of the index amputation was evaluated with the Charlson Comorbidity Index (33). We divided the patients into three groups, according to the Charlson Comorbidity Index: 0-1, 2, and 3+, where a higher score predicted an increased risk of mortality. The prescribed medications were defined as medications that were picked up from the pharmacy at least once each year. The prescribed medications were grouped according to ACT codes. The coding and the classifications of drugs were defined by the authors and validated by consensus agreement among three pharmacists who did not participate in the study, see supplementary material.

The NPR registry contains only information on diagnoses recorded during hospitalisation, and not by GPs. Therefore, central diseases were defined by combining the prevalence of the medication (ACT- codes) collected from the pharmacy with the registered diagnosis (ICD-10 codes) from hospitals: diabetes^{comb}, atherosclerosis^{comb}, cardiovascular diseases^{comb} and hypertension^{comb} (see supplementary material). A visit to a GP was defined as a show-up at the GP clinic, visits to outpatient clinics included only clinics at the hospitals while a visit to a medical specialist only includes private clinics.

Ethical approval

This register-based study included only anonymous data from national registries and had no patient contact. The scientific board of Statistics Denmark and “Statens Serum Institut” approved the study (project no 704122).

Statistics

Descriptive data, comorbidities, and the use of medication for each of the amputation groups were expressed as frequencies with percentages, for categorical data, or as median and

intraquartile range (IQR = 25th to 75th percentile) for continuous data. A comparison between major and minor amputations was made with a χ^2 test, for categorical data, and a Kruskal-Wallis test for continuous data. Diagnoses and relevant medications were compared between amputation types and atherosclerosis, diabetes, hypertension and between cardiovascular disease (CVD), diabetes and patients without. The prevalence of diagnoses and use of medications over time are depicted as graphs of the proportions of patients with a given disease, and the proportion that used a given medication, respectively. The difference in prevalence over time is expressed as percent point (pp). The data analysis was performed with SAS 9.4, and the cumulative incidence plots were constructed with R 3.2.2. Graphs of the progression over time were created with GraphPad Prism 6.07, and the flowchart was created in PowerPoint 2010. P-values less than 5% were considered significant.

Results

A total of 3375 patients underwent an LEA in Denmark during 2010 and 2011. Of these, 4% required LEAs due to trauma, and were excluded from the cohort (Figure 1). Additionally, 352 patients (11%) were excluded, due to a previous amputation on the same or opposite leg, at the same or a higher level, leaving 2883 patients who fulfilled the criteria for undergoing an index amputation during 2010 and 2011. Major amputations were performed in 1782 patients (62%), and minor amputations were performed in 1101 patients (38%). Patient characteristics are presented in Table 1. Among patients with major amputations, 1562 (88%) had not received previous amputations. Among the 266 patients with previous amputations (on a lower level), 101 patients (38%) were bilaterally amputated.

Comorbidities and medical treatment in the year of amputation

Patient diagnoses and current medications that were recorded at the time of the index amputation are presented in Table 2 and 3. Both diabetes and atherosclerosis were diagnosed in 32% of patients (577/1782) with major amputations and 35% of patients (382/1101) with minor amputations. A subgroup analysis of characteristics, comorbidities and medical treatment among patients diagnosed with either CVD including arteriosclerosis, diabetes or neither are presented in Table 4. A total of 2350 (82%) patients were diagnosed with CVD of which 1185 had CVD without diabetes and 1451 patients were diagnosed with diabetes of which 286 were not diagnosed with CVD. Furthermore, among patients diagnosed with atherosclerosis, 42% (851/2017) had not received cholesterol-lowering drugs at the time of amputation. The absence of cholesterol-lowering treatment was observed significantly more among patients with major amputations than among those with minor amputations, (46% (650/1428) vs 34% (201/589); p< 000.1). Among patients diagnosed with cardiovascular diseases (CVD) and patients diagnosed with diabetes, had 46% (543/1185) and 65% (940/1451) received cholesterol-lowering before the amputation, see Table 4. Among patients diagnosed with diabetes, 225 patients (16%) did not at any time receive

insulin or blood glucose-lowering drugs preceding the amputation. The absence of antidiabetic treatment prior to the amputation was observed significantly more often among patients with major amputations than among patients with minor amputations (19% (134/697) vs 13% (91/710), p <.001).

Disease progression and medications during the 14 years prior to amputation

Figure 2 shows the gradual increases in the proportion of patients with the most common diagnoses (atherosclerosis, diabetes, and hypertension) recorded during hospitalisations and the medications used (including antithrombotic agents, cholesterol-lowering treatments, antidiabetic drugs, and antihypertensive therapies) during the 14 years prior to the amputation. Among patients undergoing major amputations, the prevalence of atherosclerosis increased from 2% to 20% over the first 13 years, and a 58 pp increase was observed during the last year preceding the amputation. During the 14 years, the use of cholesterol-lowering drugs increased from 3% to 50%. There was a 28 pp difference between patients diagnosed with atherosclerosis who received cholesterol-lowering treatment or not prior to the amputation. Furthermore, the use of antithrombotic drugs increased from 15% to 65% during the first 13 years, and the use further increased by 6 percent point in the last year (Figure 2a). Among patients with minor amputations, the prevalence of diabetes increased from 8% to 40%, and antidiabetic treatments increased from 29% to 55%. During the last year, the prevalence of diabetes increased by 21 percent point, and the gap between treatment and diagnosis was only 3 percent point prior to minor amputation (Figure 2b). Antihypertensive treatments increased from 23% to 60% during the first 13 years, and then dropped slightly, by 4 percent point, in the last year prior to a major amputation. Similarly, antihypertensive treatments increased from 20% to 64% over the 14 years prior to minor amputations (Figure 2c).

The estimated disease progressions, calculated as the combination of the diagnosis prevalence and the medication prevalence, are presented in Figure 3. The progression of

diseases prior to a major amputation increased as follows: atherosclerosis[comb] increased from 5% to 53% during the 14 years, with a 16 percent point increase in the last five years preceding amputation; hypertension[comb] increased from 23% to 63%; cardiovascular diseases[comb] increased from 22% to 70%; and diabetes[comb] increased from 17% to 35%. The use of opioids increased from 10% to 45%, with an 18 percent point increase the last five years prior to amputation. Further, 32% received prescribed opioids three years prior to major amputation (Figure 3a). Among patients with minor amputations, the prevalence of atherosclerosis[comb] increased from 3% to 51% during the 14 years; cardiovascular diseases[comb] increased from 16% to 63%; hypertension[comb] increased from 20% to 66%; and diabetes increased from 29% to 57%. The use of opioids increased from 9% to 34%, with a 12 percent point increase in the last five years (Figure 3b). In total, 29 % received opioids three years before the amputation.

Contacts made to hospitals and GPs during the 14 years prior to amputation

Patients' visits to the healthcare system (hospitals, outpatient clinics, and GPs) during the 14 years prior to amputation are presented in Figure 3. 98% of the patients contacted healthcare services at least once during the last year prior to amputation. The proportion of patients contacting their GPs increased from 85% to 97% and the mean number of visits to GPs per year increased from 4.5 to 7.7 visits. The proportion of patients attending outpatient clinics increased from 25% to 76%, and the mean visits to outpatient clinics per year increased from 0.4 to 3.2 visits. During the last year prior to amputation, 2% of the patients had no contact with GPs or hospitals, 1% had only contacted hospitals, and 18% had only contacted GPs.

Among 851 patients diagnosed with arteriosclerosis without receiving cholesterol-lowering drugs at any time prior to the amputation, 87% had visited their GP, 29% had called out-of-hours care, 47% had been hospitalised, 70% had visited outpatient clinics, and 29% had visited the emergency room during the last year prior to amputation.

Cumulative incidences of death and re-amputation

Figure 4 shows the cumulative incidences of death and re-amputation for first year after LEA. The hazard ratios for death the first year after an AKA (compared to foot amputation) were 4.41 (95%CI: 3.44-5.66, p<0.001) with no adjustments, 3.39 (95%CI: 2.64-4.37, p<0.001) after adjusting for demographics (gender, age, social status and living arrangement), and 4.0 (95%CI: 3.09-5.19, p<0.001) after also adjusting for co-morbidities (diabetes, arteriosclerosis, hypertension, and use of opioids). The hazard ratios for death the first year after a BKA (compared to foot amputation) were 2.57 (95%CI: 1.97-3.19, p<0.001) without adjustments, 2.28 (95%CI: 1.75-2.97, p<0.001) after adjusting for demographics, and 2.39 (95%CI: 1.83-3.13, p<0.001) after also adjusting for co-morbidity.

The hazard ratios for re-amputation the first year after an AKA were 4.16 (95%CI: 3.24-5.34, p<0.001) without adjustments, 3.20 (95%CI: 2.49-4.13, p<0.001) after adjusting for demographics, and 3.69 (95%CI: 2.85-4.79, p<0.001) after also adjusting for co-morbidity. The hazard ratios for death the first year after a BKA were 2.64 (95%CI: 2.02-3.43, p<0.001) without adjustments, 2.34 (95%CI: 1.79-3.05, p<0.001) after adjusting for demographics, and 2.4 (95%CI: 1.83-3.14, p<0.001) after also adjusting for co-morbidity.

Discussion

This study showed that the prevalence of atherosclerosis was 70% and the prevalence of diabetes was 49% in an unselected national cohort of patients undergoing LEAs. Among patients with atherosclerosis, 42% had not received cholesterol-lowering treatments, although 87% of these patients had visited their GP within the preceding the amputation. Additionally, 16% of the patients with diabetes were diagnosed with diabetes the year of the amputation. The majority of patients (85% - 97%) had a contact to their GP within the 14 years prior to amputation, and 64% were in contact with a hospital outpatient clinic within the three years prior to amputation. Moreover, 88% of patients undergoing major extremity amputation had no previous amputation on a lower level. Additionally, only 6% of patients in

this cohort had undergone revascularisation prior to amputation. Nevertheless, one out of three patients received prescribed opioids three years prior to amputation. Traditionally, LEA has been associated with long-term complications of diabetes. However, the prevalence of cardiovascular diseases are increasing in western countries; consequently, the traditional perceptions must be redefined to identify risk factors for LEA. In our national cohort of patients with major amputations, the majority (83%) was diagnosed with atherosclerosis, and less (33%) had diabetes. In comparison, patients with minor amputations had a higher prevalence of diabetes (64%) and lower prevalence of atherosclerosis (53%). Similar distributions were identified by The Global Lower Extremity Amputation Study Group, 2000 (16).

According to the guidelines, our results indicate a suboptimal treatment of atherosclerosis and identification of diabetes. There was a 28 percent point difference between the proportion of patients who received cholesterol-lowering drugs and the proportion of patients diagnosed with atherosclerosis. Also, among patients with diabetes, there was a six percent point gap between patients having diabetes and patients receiving anti-diabetic treatment, indicating an unsolved clinical problem in identifying atherosclerosis and diabetes. Indeed, timely treatment might have saved these patients from an extremity amputation. The lack of recognition of symptoms related to PAD among both patients and health care professionals may be linked to a lack of knowledge inhibiting patients to react on symptoms and consult their GP in time (34). Additionally, only 6% of the patients had received revascularisations (angioplasty or bypass) prior to the index amputation. These results were concering as revascularisation surgery still is an essential part of the treatment for critical ischaemia in lower extremities (35,36). Similarly, Moxey et al. also found a low prevalence of revascularisation of 9% in an unselected, nationwide cohort (37). However, Ahmad et al. found a 30% prevalence of revascularisation in an unselected population cohort in England (11). Ahmad et al. also demonstrated demographic variations in the prevalence of

amputations and revascularisations, which were associated with social inequalities and the presence of chronic diseases.

The results of this study point towards several possibilities for preventing LEA. The finding that 29% of the patients received intensive pain treatment already three years prior to major amputation indicate symptoms of critical extremity ischaemia. For comparison, 2.6 % of the Danish population collected prescribed opioids in 2011 (38). Thus, it is essential that distal lower extremity pain should be recognised as a symptom of PAD to ensure that patients are referred to specialists to confirm the diagnosis (39,40). In Denmark, ankle and toe blood pressure are measured to calculate the Ankle-Brachial Index (ABI) (41), a non-invasive diagnostic test for PAD (42). This procedure is mainly performed at the hospitals, and rarely by the GP. Throughout the 14 years preceding amputation, the majority of patients in this study had regular and increasing contact with their GPs (prevalence increase from 85% to 97%).Thus, early identification might be feasible because patients do seek medical advice in the years prior to amputation. Furthermore, the proportion of patients in contact with outpatient clinics or were admitted to hospital increased from 25% and 76% and form from 32% to 49% during the 14 years preceding the amputation. Buckley et al. followed patients with diabetes for seven years prior to LEA and concluded a need for early referral to specialists to reduce the risk of LEA (23). It has been suggested that PAD screening could be performed with non-invasive methods like the ABI (43). Other studies have indicated that routine screening could promote preventive treatment and that a screening strategy could cost-effectively prevent the progression of PAD and cardiovascular events (44,45). Alternatively, Brand (46) and Boulton et al. (47) have suggested that a simple clinical examination of a patient's feet could indicate a need to confirm PAD. Thus, treatment could be initiated (including specialist referrals) to prevent ulcers due to ischaemia, and thus, prevent LEA. This study supports the conclusion made by Jones et al. that calls for

education programs to focus on prevention and early identification to ensure adequate treatment for preventing LEA (5).

In this study, the majority of patients (92%) had no history of previous amputation preceding the index major amputation. Heyer et al. reported that 92 % of their patients had no previous amputation based on data from health insurance companies (12) and Buckley et al. found that 28% of a selected cohort of patients with diabetes had a history of amputations (23). The present study confirms that the risk of death is highest among patients with major amputation. In contrast, neither demographics nor comorbidities could explain the high risk of death. Thus, other factors must affect the outcome after LEA, such as the general health status and the nutritional status of a patient. Also, factors related to the perioperative treatment, like a delay to surgery, could have a negative impact on the outcome (48). Similar results were reported by Jones et al., Hoffstad et al., and Wiessman et al., who called for more comprehensive, multidisciplinary efforts (5,7,10).

The strength of this study was the use of a national cohort based on the national registry, which contained information recorded over a period of 14 years before the amputation. Furthermore, we could crosslink data in various registries at an individual level, which made it possible to follow patients over time. The main limitation was the lack of a control group. An age-, sex-, and geographically-matched control group could allow differentiation between disease progression due to ageing and disease progression that leads to amputation. An inherent limitation was that the data did not allow for an estimation of patient compliance with the prescribed medication. Further, it was not possible to access neither the diagnosis recorded by the GP, as these data are not included in the national registry, nor the indication for the prescribed medication as this has just recently been included in the registry. Finally, data on examinations such as ABI prior to the amputation would have provided a more comprehensive overview of the limb-saving procedure.

Conclusion

In this study, one third of patients with LEA were living with undiagnosed or untreated atherosclerosis and one out of six were living with undiagnosed diabetes despite a regular contact with their GPs and outpatient clinics for several years prior to the amputation. For the majority of patients undergoing major LEAs, the amputation was a first-time amputation. Additionally, only a small number of patients underwent extremity-saving procedures, although one in three had received opioid prescriptions several years before the amputation. The overall findings of this study suggest that the need for opioids, combined with the presence of hypertension, diabetes, or another cardiovascular disease, could be an indication of PAD which is highly associated with lower extremity amputation. Further, clinicians are encouraged to initiate medical treatment supplemented with a careful inspection of the patient´s feet as this non-invasive examination may detect an early indication of low circulation.

Acknowledgements

We acknowledge the contribution from Research Services, Statistics Denmark and thank Jørn K Petersen for his assistance. We especially thank Nasrin Faqir, for her contribution to data management and analysis.

Competing interest

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests

Funding

This study was funded by The Novo Nordic Foundation grant number NNF12OC0002017, and Copenhagen University Hospital, Hvidovre Research Foundation. None of the sponsors were involved in the design of the study, collection, analysis, interpretation of data and in writing the manuscript.

Consent for publication

Not applicable

Data sharing statement

The datasets supporting the conclusions of this article are available in the Statistics Denmark, http://www.dst.dk/. Statistics Denmark managed and provided the secured access In according to Danish regulations, data are available by applying Statistics Denmark.

Author contributors

SJ and JP describe the study. PSJ and OA ensured funding. PSJ, JP, KKM, IP and OA designed the study. PSJ and JP applied for data at Statistics Denmark. PSJ and JP provided the statistical expertise. IP, KKM and OA provided the clinical and medical expertise. PSJ and JP performed the data management and analysis. All authors helped interpret the data. The accuracy of data and analysis was reviewed by all authors who can take responsibility for the integrity of the data and the accuracy of the data analysis. PSJ drafted the

manuscript. All authors reviewed and critically revised the manuscript for intellectual content and approved the final version of the manuscript.

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Table 1. Characteristics of patients with lower extremity amputations in 2010-2011 in Denmark

		Major amputation		Minor amputation
	Total N (%)	Above-Knee N (%)	Below-Knee N (%)	N (%)
n	n=2883	n = 1024	n=758	n=1101
Gender				
Male	1811 (63)	544 (53)	489 (65)	778 (71)
Age				
Men, median (IQR)	69 (61;79)	74 (66;82)	70 (60;78)	66 (58;76)
Women, median (IQR)	78 (68;86)	81 (72;87)	78 (68;85)	72 (63;82)
Social status[1]				
Married[2]	1165 (40)	378 (37)	307 (41)	480 (44)
Divorced	937 (32)	293 (29)	247 (33)	397 (36)
Widow	767 (27)	352 (34)	200 (26)	217 (20)
Economic status				
Working	257 (9)	24 (2)	62 (8)	171 (16)
Retired	2055 (71)	845 (83)	534 (71)	676 (61)
Social welfare	571 (20)	155 (15)	162 (21)	254 (23)
Living arrangement				
Living alone	1514 (53)	595 (58)	402 (53)	517 (47)
Living in rural areas	1705 (59)	634 (62)	431 (57)	640 (58)
Education				
< 9 year of school	2549 (88)	896 (88)	662 (87)	9991 (90)
Charlson Index				
0-1	546 (19)	196 (19)	133 (17)	217 (20)
2	456 (16)	217 (21)	105 (14)	134 (12)
3	1881 (65)	611 (60)	520 (69)	750 (68)
Multi-morbidities and Polypharmacy				
Co-morbidities[3], median (IQR)	7 (5;9)	6 (5;9)	7 (5;10)	7 (4;9)
Drugs[4], median (IQR)	7 (5;9)	7 (5;9)	7 (5;9)	6 (4;8)
Peripheral vascular procedure				
Angioplasty	89 (3)	7 (1)	4 (1)	78 (7)
Bypass graft	97 (3)	5 (0,5)	4 (1)	88 (8)
Surgery history				
Previous amputation	266 (9)	113 (11)	107 (14)	46 (4)
< 3 amputations	203 (7)	84 (8)	76 (14)	43 (4)
≥ 3 amputations	63 (2)	29 (3)	31 (4)	3 (-)

Values represent the number of patients (%), unless indicated otherwise. [1]Missing n=12. [2]Married or residing with a partner. [3]All ICD10 diagnoses. [4]ACTcodes for main groups

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Table 2. Prevalence of comorbidity among patients with lower extremity amputations in 2010-2011 in Denmark

	Major amputations			Minor amputations	
	Total, N (%)	Above Knee n (%)	Below Knee n (%)	Total, N (%)	P value*
	N=1782	N=1024	N=758	N=1101	
Peripheral Vascular Disorders	1481 (83)	873 (85)	608 (80)	625 (57)	<.0001
Atherosclerosis[1]	1428 (80)	844 (82)	584 (77)	589 (54)	<.0001
Hypertension[2]	902 (51)	577 (56)	441 (58)	599 (54)	.18
Diabetes[2]	697 (39)	331 (32)	366 (48)	710 (64)	<.0001
Diabetic foot ulcer[3]	505 (18)	224 (22)	281 (37)	522 (47)	<.0001
Neuropathy[3]	174 (6)	69 (7)	105 (14)	230 (21)	<.0001
Retinopathy[3]	112 (6)	37 (4)	75 (10)	141 (13)	<.0001
Nephropathy[3]	85 (5)	22 (2)	63 (8)	82 (7)	.0028
Cardiac ischaemia[3]	597 (34)	348 (34)	249 (33)	329 (30)	.04
Cardiac Arrhythmia	536 (30)	319 (31)	215 (28)	232 (21)	<.0001
Cerebrovascular disease[4]	540 (30)	317 (31)	223 (29)	195 (18)	<.0001
Congestive Heart Failure	401 (23)	228 (22)	173 (23)	191 (17)	.0009
Stroke[3]	401 (23)	234 (23)	167 (22)	144 (13)	<.0001
Arthrosis[3]	320 (18)	202 (20)	118 (16)	195 (18)	.86
Chronic Pulmonary Diseases	356 (20)	227 (22)	129 (17)	129 (12)	<.0001
Fluid & electrolyte disorders	330 (19)	211 (21)	119 (16)	123 (11)	<.0001
Emboli[3]	359 (20)	231 (23)	128 (17)	88 (8)	<.0001
Renal Failure	252 (14)	129 (13)	123 (16)	133 (12)	.11
Tumor without Metastasis	243 (14)	143 (14)	100 (13)	107 (10)	.0018
Alcohol addiction	227 (13)	121 (12)	106 (14)	122 (11)	.18
Obesity	130 (7)	60 (6)	70 (9)	127 (12)	.0001
Rheumatoid Arthritis	139 (8)	77 (8)	62 (8)	90 (8)	.71
Depression	124 (7)	77 (8)	47 (6)	58 (5)	.069
Dementia[5]	110 (6)	69 (7)	43 (6)	37 (3)	.0006
Liver disease	79 (4)	40 (4)	39 (5)	51 (5)	.80
Metastatic Cancer	50 (3)	36 (3)	14 (2)	9 (1)	.0002
Weight loss	43 (2)	30 (3)	13 (2)	12 (1)	.0155
Bone Cancer[3]	24 (1)	14 (1)	10 (1)	2 (-)	.0013

*P<0.05, major vs. minor amputation. Comorbidity, defined according to Elixhauser Comorbidity index;[1] includes only ICD10- I170; [2] includes uncomplicated and complicated conditions; [3] not included in the Elixhauser Comorbidity index; [4]included from the Charlson Comorbidity index

Table 3. Prevalence of prescribed medications used by patients with lower extremity amputations in 2010-2011 in Denmark

	Major amputations			Minor amputations	
	Total, N (%)	Above Knee n (%)	Below Knee n (%)	Total, N (%)	P value*
	N=1782	N=1024	N=758	N=1101	
Opioids	1484 (83)	876 (86)	608 (80)	684 (62)	<.0001
Antithrombotic drugs	1262 (71)	738 (72)	524 (69)	711 (65)	.0005
Acetaminophen	1333 (75)	802 (78)	531 (70)	621 (56)	<.0001
Antihypertensives	1000 (56)	577 (56)	423 (56)	715 (65)	<.0001
Cholesterol-lowering drugs	886 (50)	481 (47)	405 (53)	627 (57)	.0002
Neuropathic pain relievers	919 (52)	517 (50)	402 (53)	330 (30)	<.0001
Antidepressants	864 (48)	501 (49)	363 (48)	365 (33)	<.0001
Antidiabetic therapy	588 (33)	268 (26)	320 (42)	638 (58)	<.0001
Beta blockers	760 (43)	440 (43)	320 (42)	439 (40)	0.14
NSAID	451 (25)	264 (26)	187 (25)	312 (28)	0.07
Drugs for airway disease	337 (19)	199 (19)	138 (18)	146 (14)	<.0001
Alcohol addiction	341 (19)	198 (20)	143 (19)	122 (11)	<.0001
Smoking cessation	259 (15)	155 (15)	104 (14)	132 (12)	.053
Cortisol	246 (14)	156 (15)	90 (12)	120 (11)	.023

*P<0.05, major vs. minor amputation

Table 4. Characteristics and comorbidities among patients with lower extremity amputation diagnosed with cardio vascular diseases, diabetes or without in 2010-2011.

	In risk of Lower limb amputation			No CVD or diabetes	
		Cardiovascular disease (CVD)	Diabetes		P value*
	N=2636	N=1185(%)	N=1451(%)	N=247(%)	
Characteristics					
Male	1680 (64)	637 (54)	1043 (72)	131 (53)	<.0001
Married	1058 (40)	430 (36)	628 (43)	107 (43)	0.0003
working	197 (7)	46 (4)	151 (10)	60 (24)	<.0001[1]
Retired	1943 (74)	985 (83)	958 (66)	112 (45)	
Social welfare	496 (19)	154 (13)	342 (24)	75 (30)	
Living in rural areas	1548 (59)	704 (59)	844 (58)	157 (64)	0.5
Charlson index, 0-1	376 (14)	322 (27)	54 (4)	170 (69)	<.0001[2]
2	411 (16)	314 (27)	97 (7)	45 (18)	
3	1849 (70)	549 (46)	1300 (90)	32 (13)	
Previous amputation	252 (10)	55 (5)	197 (14)	14 (6)	<.0001
Multi-morbidities					
Co-morbidities, median (IQR)	8 (6;10)	6 (5;8)	10 (7;12)	1 (0;2)	<.0001
Drugs, median (IQR)	7 (5;9)	6 (4;8)	8 (6;10)	3 (2;5)	<.0001
Ulcer	1360 (52)	489 (41)	871 (60)	80 (32)	<.0001
Hypertension	1397 (53)	519 (44)	878 (61)	34 (14)	<.0001
Arthrosis	454 (17)	227 (19)	227 (16)	61 (25)	0.02
Chronic Pulmonary Diseases	466 (18)	250 (21)	216 (15)	19 (8)	<.0001
Tumour without Metastasis	310 (12)	178 (15)	132 (9)	40 (16)	<.0001
Alcohol addiction	319 (12)	156 (13)	163 (11)	30 (12)	0.1
Obesity	252 (10)	28 (2)	224 (15)	5 (2)	<.0001
Rheumatoid Arthritis	203 (8)	110 (9)	93 (6)	26 (11)	0.006
Liver disease	109 (4)	41 (3)	68 (5)	21 (9)	0.1
Metastatic Cancer	52 (2)	40 (3)	12 (1)	7 (3)	<.0001
Prescribed medication					
Opioids	2027 (77)	93 (84)	1034 (71)	141 (57)	<.0001
Cholesterol-lowering drugs	1483 (56)	543 (46)	940 (65)	30 (12)	<.0001
Antithrombotic drugs	1919 (73)	855 (72)	1064 (73)	54 (22)	0.5
Antihypertensive	1647 (62)	611 (52)	1036 (71)	68 (28)	<.0001
Neuropathic pain relievers	1162 (44)	580 (49)	582 (40)	87 (35)	<.0001
Beta blockers	1161 (44)	475 (40)	686 (47)	38 (15)	.0002
Alcohol addiction	420 (16)	226 (19)	194 (13)	43 (17)	<.0001
Drugs for airway disease	459 (17)	240 (20)	219 (15)	24 (10)	.0005

*P<0.05, Cardiovascular disease vs diabetes.
CVD includes Atherosclerosis, Peripheral Vascular Disorders, Cardiac ischemia, Emboli, Stroke, Cerebrovascular disease. Diabetes includes antidiabetic therapy.
[1]P value represents the distribution of working, retired and social welfare between patients with CVD, diabetes or without.
[2] P value represents the distribution of Charlson Index between patients with CVD, diabetes or without.

Figures titles and legends

Figure 1

Title: Figure 1. Flowchart shows study selection of patients with lower extremity amputations between 01.01.2010 -31.12.2011 in Denmark

Legends: (1) Excluded due to previous amputation define as amputation on the same level or bilateral amputation on a higher level than the index amputation in 2010-11; (2) include hip-exarticulation; (3) include knee disarticulation.

Figure 2

Title: Figure 2. The prevalence of comorbidities and prescribed medications during the 14 years preceding major and minor lower extremity amputations.

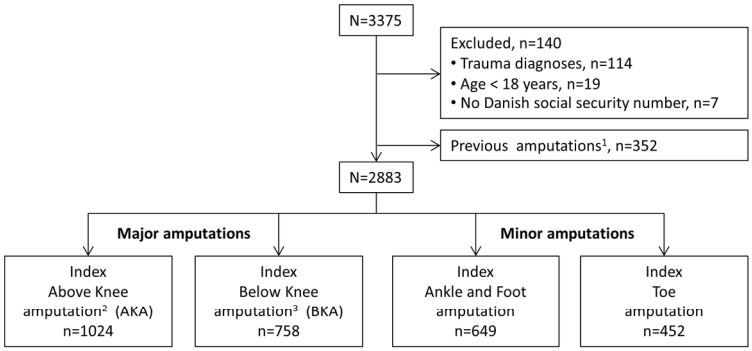
Figure 3

Title: Figure 3. 14 years of estimated progression of chronic diseases and contacts to healthcare system preceding (a,c) major and (b,d) minor lower extremity amputations

Legends: The prevalence of comorbidities, defined by both ICD-10 coding and the use of prescribed medications (ACT code), was estimated each year.

Figure 4

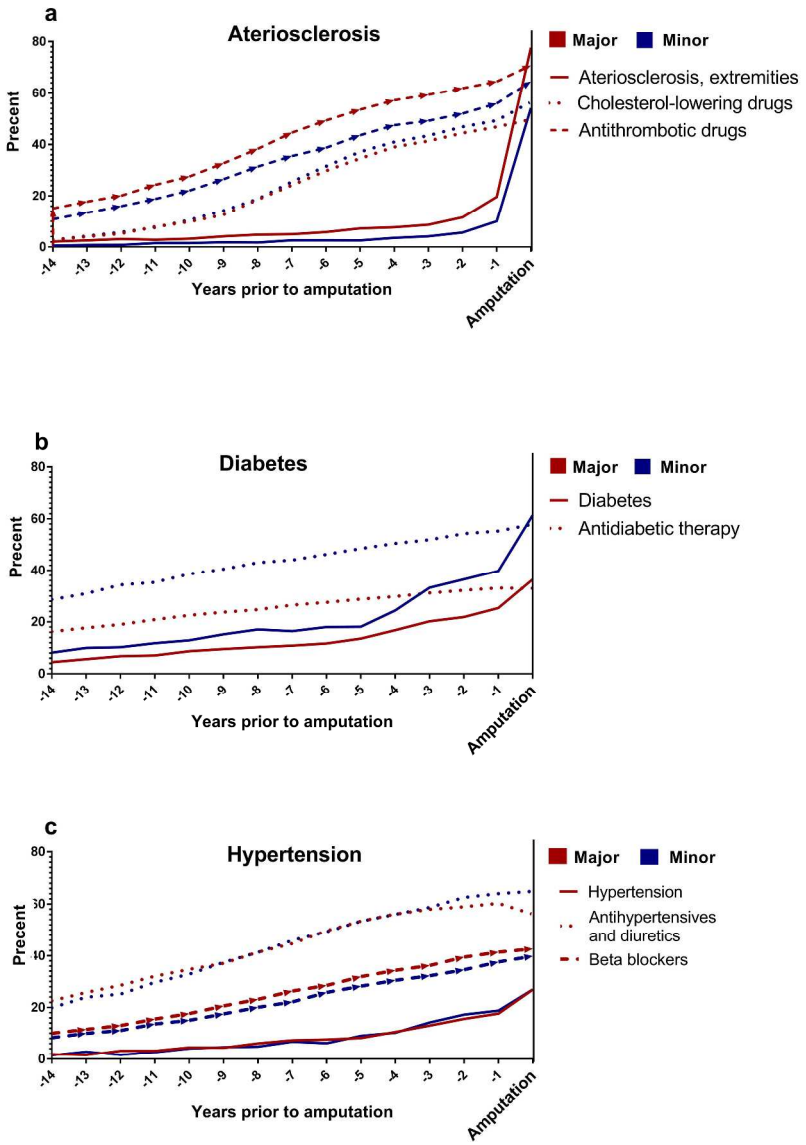
Title: Figure 4. One-year cumulative outcomes. The cumulative probabilities of (*left*) re-amputation procedures and (*right*) survival are shown for patients that received major (AKA and BKA) and minor lower extremity amputations



Title: Figure 1. Flowchart shows study selection of patients with lower extremity amputations between 01.01.2010 -31.12.2011 in Denmark

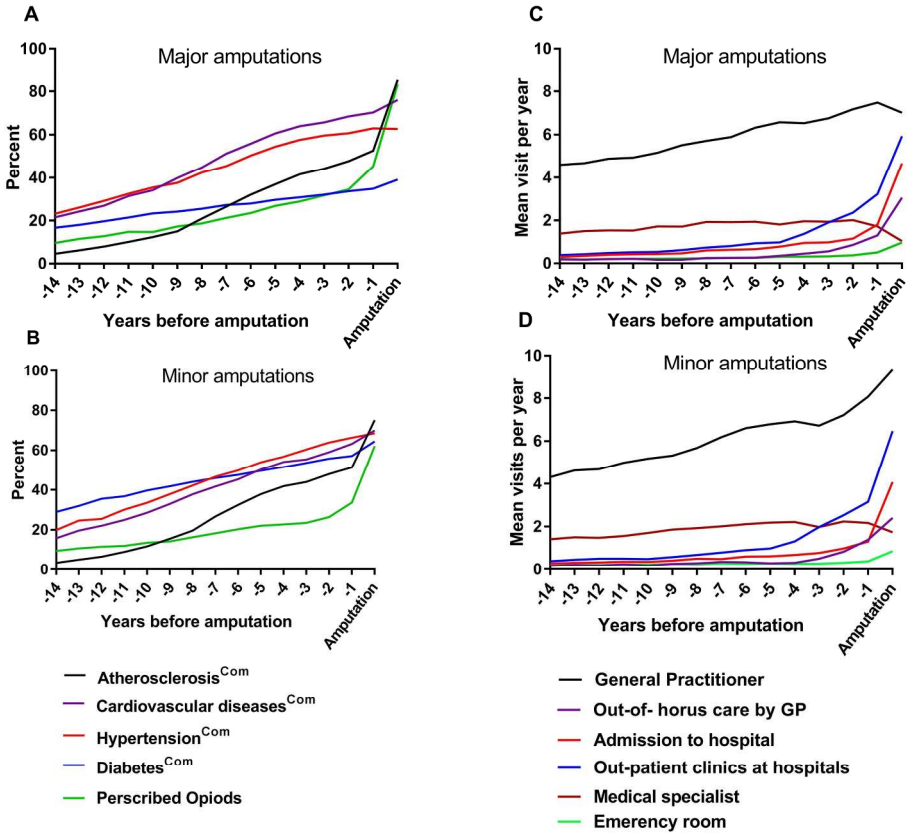
Legends: (1) Excluded due to previous amputation define as amputation on the same level or bilateral amputation on a higher level than the index amputation in 2010-11; (2) include hip-exarticulation; (3) include knee disarticulation.

190x142mm (300 x 300 DPI)



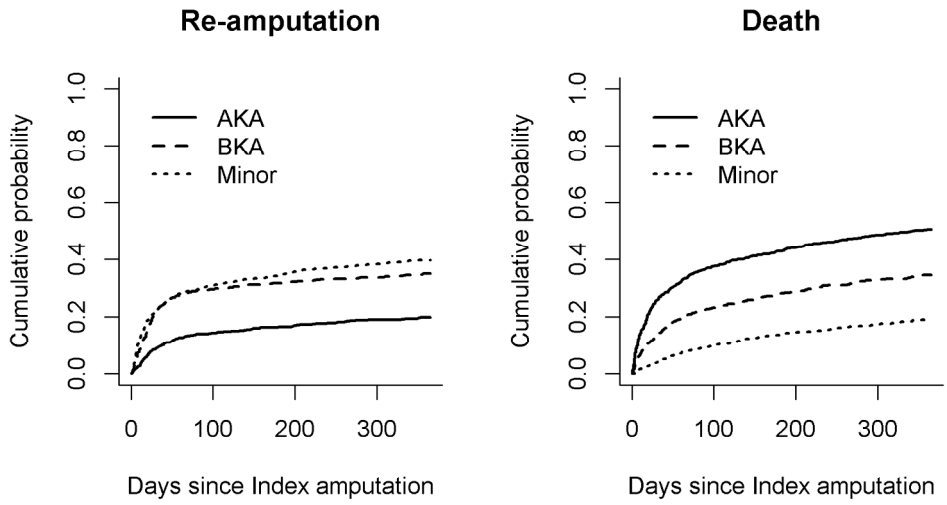
Title: Figure 2. The prevalence of comorbidities and prescribed medications during the 14 years preceding major and minor lower extremity amputations.

285x396mm (300 x 300 DPI)



Title: Figure 3. 14 years of estimated progression of chronic diseases and contacts to healthcare system preceding (a,c) major and (b,d) minor lower extremity amputations
Legends: The prevalence of comorbidities, defined by both ICD-10 coding and the use of prescribed medications (ACT code), was estimated each year.

206x184mm (300 x 300 DPI)



Title: Figure 4. One-year cumulative outcomes. The cumulative probabilities of (left) re-amputation procedures and (right) survival are shown for patients that received major (AKA and BKA) and minor lower extremity amputations

177x101mm (300 x 300 DPI)

Progression of disease preceding lower extremity amputation in Denmark: A longitudinal registry study of diagnoses, use of medication and healthcare services 14 years prior to amputation

Supplementary material

SKS codes for surgical procedure, identification of index amputation

Above Knee Amputation (AKA)	
Hip-exarticulation	(KNFQ09)
Trans-Femoral amputation	(KNFQ19, KNFQ99)
Below Knee Amputation (BKA)	
Knee disarticulation	(KNGQ09)
Trans-Tibial amputation	(KNGQ19, KNGQ99)
Foot amputation	(KNHQ00-08)
Toe amputation	(KNHQ10-18, KNHQ 90-99)

Rank of amputation procedure

1. Hip-exarticulation	(KNFQ09)
2. Trans-Femoral amputation	(KNFQ19, KNFQ99)
3. Knee disarticulation	(KNGQ09)
4. Trans-Tibial amputation	(KNGQ19,KNGQ99)
5. Foot amputation	(KNHQ10-18, KNHQ 90-99)
6. Revision of stump or related amputation procedure after Hip-exarticulation or Trans-Femoral amputation	(KNFQ29, KNFQ39, KNFQ49)
7. Revision of stump or related procedure after Knee disarticulation or Trans-Tibial amputation	(KNGQ29, KNGQ39, KNGQ49)
8. Toe amputation	(KNHQ00-08)
9. Stump revision of foot or toe amputation	(KNHQ20-28)

Progression of disease preceding lower extremity amputation in Denmark: A longitudinal registry study of diagnoses, use of medication and healthcare services 14 years prior to amputation

ICD10 code for diagnosis

Atherosclerosis	DI70
Atherosclerosis, extremities	D1702
Diabetes	
Neuropathy	DE104, DE114, DE124, DE134, DE144
Retinopathy	DE103, DE113, DE123, DE133, DE143
Nephropathy	DE102, DE122, DE132, DE142
Foot ulcer	DE105, DE115, DE125, DE135, DE145
Ulcer	Dl97, DL88, Dl89, DL984, DS91, DR02, DL02
Apoplexia	DI60, DI61, DI62, DI63, DI64
Emboli	DI80, DI81, DI82, DI74
Bone cancer	DC40, DC41, DC49
Arthrosis	DM15, DM16,DM17, DM18, DM19

ACT codes for medication

Antidiabetic therapy	
Insulins	A10A
Blood Glucose lowering drugs	A10B
Antithrombotic drugs	B01A
Drugs for hypertension	
Antihypertensives	C02DB, C02CA, C08, C09
Diuretics, Thiazides, plan	C03AA - Eller hele gruppen C03 Diuretics ?
Beta blockers	C07
Cholesterol-lowering drugs	C10AA, C10AB, C10AD, C10AX, C10B
Corticosteroids for systemic use	H02A
Obstructive airway disease	R03
Opioids	N02A
Codeine	R05DA04
Acetaminophen	N02B
NSAID	M01A
Neuropathic pain relievers	
Antiepileptics drugs	N03AX
Antidepressants	N06AA, N06AX
Drugs for alcohol addiction	N07BB, N03AA, N05BA
Drugs for smoking cessation	N07BA, N06AX,

Progression of disease preceding lower extremity amputation in Denmark: A longitudinal registry study of diagnoses, use of medication and healthcare services 14 years prior to amputation

Codes used to estimate the progression of diseases over 14 years prior to amputation by combining diagnosis and prescribed medication

Atherosclerosis[Com]	
Arteriosclerosis	ICD code DI70
Cholesterol-lowering drugs	ACT code C10AA, C10AB, C10AD, C10AX, C10B
Diabetes[Com]	
Diabetes	ICD code DE10, DE11, DE12, DE13, DE14
Antidiabetic therapy	ACT code A10A, A10B
Cardiovascular diseases[Com]	
Cardiac ischemia	ICD code DI20, DI21, DI22, DI23, DI24, DI25,
Congestive heart failure, cardiac arrhythmia,	Elx_GRP_1, ELX_GRP_2
Beta blockers, Antithrombotic drugs	ACT code C07, B01A
Hypertension[Com]	
Hypertension	ICD code DI10, DI11, DI12, DI13, DI,15
Drugs for hypertension	ACT code C02DB, C02CA, C03AA, C08, C09
Prescribed opioids	
ACT code, opioids	ACT code N02A, R05DA04

Subgroup analysis according to diseases

CVD	
Arteriosclerosis	ICD code DI70
Cardiac ischemia	ICD code DI20, DI21, DI22, DI23, DI24, DI25,
Congestive heart failure, cardiac arrhythmia,	Elx_GRP_1, ELX_GRP_2
Emboli	DI80, DI81, DI82, DI74
Stroke	DI60, DI61, DI62, DI63, DI64, DG45, DG46
Cerebrocardiovascular disease	CC_GRP_4
Diabetes:	
Diabetes[Com]	
In risk of LEA	
Group "CVD" and "Diabetes[Com]" combined	
No CVD or Diabetes	
Patient not included in the group "In risk of LEA"	

Note: ELX_GRP_x refers to The Elixhauser Comorbidity Index, CC_GRP_X refers to Charlson Comorbidity Index

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page, p 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 8
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9
		(*b*) Describe any methods used to examine subgroups and interactions	Page 9
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 10, (Figure 1)
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 10, (Table1)
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 11-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 13
		(*b*) Report category boundaries when continuous variables were categorized	Tabel 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 14,15,16
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.