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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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3 1 **Title**

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6 2 Progression of disease preceding lower extremity amputation: A longitudinal registry study of
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8 3 diagnoses, use of medication and healthcare services 14 years prior to amputation

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28 **Word count:** 3951

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2
3 29 **Abstract**
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6 30 **Objectives:** Patients with non-traumatic lower extremity amputation are characterised by
7
8 31 high age, multi-morbidity and polypharmacy and long term complications of atherosclerosis
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10 32 and diabetes. To ensure early identification of patients at risk of amputation, we need to gain
11
12 33 knowledge about the progression of diseases related to lower extremity amputations during
13
14 34 the years preceding the amputation.

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16 35 **Design:** A population-based national registry study.
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19 36 **Setting:** The study includes data on demographics, diagnoses, surgery, medications, and
20
21 37 healthcare services from five national registries. Data were retrieved from 14 years before
22
23 38 until 1 year after the amputation. Descriptive statistics were used to describe progression of
24
25 39 diseases and use of medication and healthcare services.
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28 40 **Participants:** An unselected cohort of patients (≥ 50 yrs; $n=2883$) subjected to a primary
29
30 41 non-traumatic lower extremity amputation in 2010 or 2011 in Denmark.
31

32 42 **Results:** The prevalence of atherosclerosis, hypertension and diabetes was 70%, 53% and
33
34 43 49%, respectively. Among patients with atherosclerosis, 42 % had not received cholesterol-
35
36 44 lowering treatment even though 87% had visited their general practitioner within the last year
37
38 45 prior to amputation. Further, 16% were diagnosed with diabetes at the time of the
39
40 46 amputation. The prevalence of cardiovascular diseases increased from 22% to 70%,
41
42 47 atherosclerosis from 5% to 53%, and diabetes from 17% to 35% over the 14 years preceding
43
44 48 major amputation. Of all patients, 64% had been in contact with the hospital or out-patient
45
46 49 clinics within the last three years and 34% had received a prescription of opioids within the
47
48 50 last year prior to the amputation.
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50
51 51 **Conclusion:** Among patients with non-traumatic lower extremity amputation, one third live
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53 52 with undiagnosed and untreated atherosclerosis and one sixth suffer from undiagnosed
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55 53 diabetes despite continuous contacts to general practitioner and the hospital. This study
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54 emphasizes a need for enhanced focus, among both hospital clinicians and general
55 practitioners, on the early identification of atherosclerosis and diabetes.

56 **Keywords** Lower extremity amputation, Atherosclerosis, Diabetes, Healthcare services

For peer review only

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3 57 **Article Summary**
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6 58 **Article focus**
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- 10 • Patients who undergo non-traumatic lower extremity amputation (LEA) are characterised
11 by high age, multi-morbidity, polypharmacy and high mortality.
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15 • To ensure early identification of patients at risk of LEA, we need to gain more knowledge
16 about the development and progression of LEA-related diseases.
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21 63 **Key messages**
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- 24 • One third of patients with LEA were living with undiagnosed and untreated
25 atherosclerosis and one out of six were living with undiagnosed diabetes despite regular
26 contact with their GPs and outpatient clinics for several years prior to amputation
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32 • Atherosclerosis is the primary comorbidity among patients undergoing major extremity
33 amputations. For the majority of patients, the major LEA is a first-time amputation.
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38 • Clinicians are encouraged to supplement medical treatment of cardiovascular diseases,
39 including pain treatment, with a careful inspection of the patient's feet as this non-
40 invasive examination may detect insufficient circulation.
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45 72 **Strengths and limitations of the study**
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49 • The strengths of this national registry study were the inclusion of data describing
50 diagnoses and use of medication and healthcare services during the last 14 years
51 preceding non-traumatic LEA performed in Denmark.
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3 76 • The main limitation was the lack of a control group. An age-, sex-, and geographically-
4
5 77 matched control group would have allowed differentiation between disease progression
6
7 78 due to aging and disease progression leading to amputation. An inherent limitation was
8
9 79 that the data did not allow an estimation of patient compliance with the prescribed
10
11 80 medication.

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14 81 **Abbreviations**

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16
17 82 LEA: lower extremities amputation

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19 83 Major LEA: Lower extremity amputation performed above the ankle level

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21 84 Minor LEA: Lower extremity amputation performed below the ankle level

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24 85 AKA: Above knee amputation

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26 86 BKA: Below knee amputation

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29 87 PAD: Peripheral artery disease

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31 88 GP: General practitioner
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89 Introduction

90 Lower extremity amputation (LEA) is a severe event associated with loss of mobility, pain,
91 decreased quality of life, major disfigurement, and increased risk of re-amputation and
92 hospitalisation (1–3). Even though the incidence of LEA has decreased worldwide over the
93 last two decades, large variations persist; from 5.8 to 31 per 10⁵ individuals in different
94 populations (4). Moreover, the reported one-year mortality rate was 12% to 58% (5–8), and
95 the highest mortality rate (45%–58%) was associated with above-the-knee amputations
96 (AKA) (9,10). Age and the severity of comorbidities are the most prominent prognostic
97 factors for mortality after LEA (6,7).

98 The most prevalent comorbidities in patients with LEA are atherosclerosis and diabetes
99 (4,11,12). Among all major amputations, approximately 50–90% are related to peripheral
100 artery disease (PAD), 20–80% are related to diabetes, and 10% to trauma (13). During the
101 last decade, the global prevalence of PAD has increased by 23%, with the highest increase
102 among low-income countries (14). The risk factors for PAD are age, smoking, history of
103 cardiovascular diseases, diabetes, hypertension, dyslipidaemia, and obesity (15). To our
104 knowledge, only one previous study has investigated the progression of LEA-related
105 diseases by examining the use of medication over a seven-year period prior to amputation
106 among patients diagnosed with diabetes (16). Buckley et al. recommended an earlier referral
107 to a medical specialist to prevent LEA. Currently, the estimated global prevalence of
108 diabetes is 9% and 90% is characterised as type 2 diabetes (17). Furthermore, the
109 prevalence of diabetes is estimated to increase by 55% over the next twenty years, which
110 represents 10% of the global population. Nevertheless, the risk of amputation remains high,
111 and some patients remain undiagnosed until it is too late to prevent LEA (18). In a cohort of
112 patients with diabetes, 18% had a cardiovascular disease with PAD being most prevalent
113 (19). Among patients diagnosed with both diabetes and PAD, the risk of amputation is 1.5
114 times higher than in patients diagnosed with PAD alone and five times higher than in

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3 115 patients only diagnosed with diabetes (20). To ensure early identification of patients at risk of
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5 116 amputation, we need more knowledge about the progression of LEA-related diseases. This
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7 117 knowledge is reflected in the historic use of medication and the need for healthcare services
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9 118 across all groups of patients with LEAs. The aim of this study was to examine the
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11 119 progression of LEA-related diseases. We examined the use of medication and the number of
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13 120 contacts with healthcare services during the 14 years leading up to LEAs, in an unselected
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15 121 population of all Danish patients that underwent LEAs. With these data, we also studied the
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17 122 associations between LEA-related diseases and the one-year prognosis after the LEA
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3 124 **Methods**
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6 125 **Setting**
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8 126 The Danish healthcare system is tax-funded and offers free and equal access to medical
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10 127 care. All citizens have a general practitioner (GP) who provides referrals to specialists and
11
12 128 hospital treatments. The GPs are responsible for their patients' medical treatment.
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14 129 Prescribed medications and other healthcare services, such as a physiotherapy etc., are
15
16 130 partly tax-funded, with a differential out-of-pocket fee.
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19 131 **Study design and data sources**
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21
22 132 We included data from the following five nationwide registries: (1) The National Patient
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24 133 Registry (NPR) which contains information on hospitalisations, including visits to outpatient
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26 134 clinics and emergency rooms (21), surgical procedures, coded according to the Nordic
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28 135 Classification of Surgical Procedures (NCSP), and diagnoses coded according to the
29
30 136 International Classification of Diseases (ICD-10); (2) The National Prescription Registry
31
32 137 contains information on prescribed medications picked up at the pharmacy (22). Medications
33
34 138 are coded according to the global Anatomical Therapeutic Chemical (ATC) classification
35
36 139 system; (3) The Danish National Health Service Registry for Primary Care (NHSR) contains
37
38 140 information on all contacts with GPs, including out-of-hours care from GPs and practising
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40 141 medical specialists(23); (4) The Danish Civil Registration System (CRS) contains information
41
42 142 on gender, date of birth, vital status, spouses and residents, (24); (5) The Attainment
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44 143 Registry contains data on education level. All Danish citizens are registered with a unique
45
46 144 personal identification number (CPR number), which allows linkage with all nationwide
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48 145 registries at an individual level. All data were provided by Statistics Denmark
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50 146 (<http://www.danmarksstatistik.dk/en>).
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3 147 ***Study cohort***
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5 148 We included patients who had undergone at least one of the following surgical procedures,
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7 149 performed between the 1st of January 2010 and 31st of December 2011: hip-exarticulation,
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9 150 trans-femoral amputation (i.e., Above-knee amputation [BKA]); knee disarticulation or trans-
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11 151 tibial amputation (i.e., below-the-knee amputation [BKA]); ankle or foot amputation; or toe
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13 152 amputation. See supplementary materials for detailed information. To eliminate trauma-
14
15 153 related amputations, we excluded patients with a trauma diagnosis recorded at any time
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17 154 prior to the amputation. We also excluded foreign patients without a CPR number and
18
19 155 patients below 18 years of age. Furthermore, to ensure homogeneity within the groups, we
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21 156 defined an index amputation as the first surgical amputation performed as an AKA, BKA,
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23 157 ankle-, foot- or toe amputation in 2010 and 2011.
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27 158 ***Categorisation of amputation procedures***
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29 159 For patients who received more than one amputation procedure on the same day, the most
30
31 160 severe procedure was identified and was used for analysis. The severity of different types of
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33 161 amputations (based on surgical codes) was ranked from the most severe procedure as hip-
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35 162 exarticulation and transfemoral amputation to the least severe as a toe amputation
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37 163 procedure. Detailed description is present in the supplementary material. When patients had
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39 164 both a left- and right-side amputation code on the same day, the procedure was categorised
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41 165 as a bilateral amputation.
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44 166 The definition of the index amputation was based on the surgical amputation procedures and
45
46 167 was divided into the following four groups: AKA, BKA, foot/ankle amputation, and toe
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48 168 amputation. AKA and BKA were classified as major amputations, and foot/ankle or toe
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50 169 amputations were classified as minor amputations.
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3 170 ***Demographics, comorbidities, medications, and contacts with healthcare services***
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5 171 For each patient, we retrieved cumulative registry information on the education level, living
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7 172 conditions, socioeconomic status, place of residence, diagnoses, prescribed medications,
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9 173 contacts with healthcare services, re-amputations, and death, which had been recorded
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11 174 between 01.01.1997 and 31.12.2012. The Elixhauser Comorbidity Index was used to identify
12
13 175 the progression of comorbidities over the 14 years prior to amputation. The Index included
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15 176 31 pre-defined comorbidities; however, in this study, we combined the pre-defined codes for
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17 177 uncomplicated and complicated diabetes and hypertension (34). To describe comorbidity,
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19 178 the Elixhauser Comorbidity Index was supplemented with ICD-10 codes for atherosclerosis.
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21 179 Further subgroups were created, including atherosclerosis in the lower extremities, diabetic
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23 180 neuropathy, retinopathy, nephropathy foot ulcer, other ulcers-not related to diabetes, stroke,
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25 181 emboli, bone cancer, and arthrosis, see supplementary material. The severity of the
26
27 182 comorbidity identified at the time of the index amputation was evaluated with the Charlson
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29 183 Comorbidity index (25). We divided the patients into three groups, according to the Charlson
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31 184 Comorbidity index: 0-1, 2, and 3+, where a higher score predicted a higher risk of mortality.
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33 185 The prescribed medications were defined as medications that were picked up from the
34
35 186 pharmacy at least once each year. The prescribed medications were grouped according to
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37 187 ACT codes (see Table 2). The coding and the classifications of drugs were defined by the
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39 188 authors and validated by consensus agreement among three pharmacists who did not
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41 189 participate in the study. See supplementary material.
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45 190 The NPR registry contains only information on diagnoses recorded during hospitalisation,
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47 191 and not by GPs. Therefore, central diseases were defined by combining the prevalence of
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49 192 the medication (ACT- codes) collected from the pharmacy with the registered diagnosis
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51 193 (ICD-10 codes) from hospitals: diabetes^{comb}, atherosclerosis^{comb}, cardiovascular diseases^{comb}
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53 194 and hypertension^{comb} (see supplementary material). A visit to a GP was defined as a show-
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55 195 up at the GP clinic and visits to outpatient clinics included only clinics at the hospitals.
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3 196 **Ethical approval**

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5 197 This register-based study included only anonymous data from national registries and had no
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7 198 patient contact. The scientific board of Statistics Denmark and “Statens Serum Institut”
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9 199 approved the study (project no 704122).

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11 200 **Statistics**

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14 201 Descriptive data, comorbidities, and the use of medication for each of the amputation groups
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16 202 (AKA, BKA, and minor amputation) were expressed as frequencies with percentages, for
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18 203 categorical data, or as median and intraquartile range (IQR = 25th to 75th percentile) for
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20 204 continuous data. A comparison between major (AKA and BKA) and minor amputations was
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22 205 made with a χ^2 test, for categorical data, and a Kruskal Wallis test for continuous data.
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24 206 Diagnoses and relevant medications were compared for atherosclerosis, diabetes, and
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26 207 hypertension. The prevalence of diagnoses and use of medications over time are depicted
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28 208 as graphs of the proportions of patients with a given disease, and the proportion that used a
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30 209 given medication, respectively. The difference in prevalence over time is expressed as
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32 210 percent point (pp). The data analysis was performed with SAS 9.4, and the cumulative
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34 211 incidence plots were constructed with R 3.2.2. Graphs of the progression over time were
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36 212 created with GraphPad Prism 6.07, and the flowchart was created in Power Point 2010. P-
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38 213 values less than 5% were considered significant.

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3 216 **Results**
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6 217 A total of 3375 patients underwent an LEA in Denmark during 2010 and 2011. Of these, 4%
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8 218 required LEAs due to trauma, and were excluded from the cohort (Figure 1). Additionally,
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10 219 352 patients (11%) were excluded, due to a previous amputation on the same or opposite
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12 220 leg, at the same or a higher level. A total of 2883 patients fulfilled the criteria for undergoing
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14 221 an index amputation during 2010 and 2011. Major amputations were performed in 1782
15
16 222 patients (62%), and minor amputations were performed in 1101 patients (38%). Patient
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18 223 characteristics are presented in Table 1. Among patients with major amputations, 1562
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20 224 (88%) had not received previous amputations. Among the 266 patients with previous
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22 225 amputations (on a lower level), 101 patients (38%) were bilaterally amputated.
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25 226 ***Comorbidities and medical treatment in the year of amputation***
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28 227 Patient diagnoses and current medications that were recorded at the time of the index
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30 228 amputation are presented in Table 2 and 3. Both diabetes and atherosclerosis were
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32 229 diagnosed in 32% of patients (577/1782) with major amputations and 35% of patients
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34 230 (382/1101) with minor amputations. Furthermore, among patients diagnosed with
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36 231 atherosclerosis, 42% (851/2017) had not received cholesterol-lowering drugs at the time of
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38 232 amputation. The absence of cholesterol-lowering treatment was observed significantly more
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40 233 among patients with major amputations than among those with minor amputations, (46%
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42 234 (650/1428) vs 34% (201/589); $p < 0.001$). Among the 1407 patients diagnosed with diabetes,
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44 235 225 patients (16%) did not at any time receive insulin or blood glucose-lowering drugs
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46 236 preceding the amputation. The absence of antidiabetic treatment prior to the amputation was
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48 237 observed significantly more often among patients with major amputations than among
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50 238 patients with minor amputations (19% (134/697) vs 13% (91/710), $p < .001$).
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3 240 ***Disease progression and medications during the 14 years prior to amputation***
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5 241 Figure 2 shows the gradual increases in the proportion of patients with the most common
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7 242 diagnoses (atherosclerosis, diabetes, and hypertension) recorded during hospitalisations
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9 243 and the medications used (including antithrombotic agents, cholesterol-lowering treatments,
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11 244 antidiabetic drugs, and antihypertensive therapies) during the 14 years prior to the
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13 245 amputation. Among patients undergoing major amputations, the prevalence of
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15 246 atherosclerosis increased from 2% to 20% over the first 13 years, and a 58 pp increase was
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17 247 observed during the last year preceding the amputation. During the 14 years, the use of
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19 248 cholesterol-lowering drugs increased from 3% to 50%. There was a 28 pp difference
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21 249 between patients diagnosed with atherosclerosis who received cholesterol-lowering
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23 250 treatment or not prior to the amputation. Furthermore, the use of antithrombotic drugs
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25 251 increased from 15% to 65% during the first 13 years, and the use further increased by 6
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27 252 percent point in the last year (Figure 2a). Among patients with minor amputations, the
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29 253 prevalence of diabetes increased from 8% to 40%, and antidiabetic treatments increased
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31 254 from 29% to 55%. During the last year, the prevalence of diabetes increased by 21 percent
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33 255 point, and the gap between treatment and diagnosis was only 3 percent point prior to minor
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35 256 amputation (Figure 2b).

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39 257 Antihypertensive treatments increased from 23% to 60% during the first 13 years, and then
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41 258 dropped slightly, by 4 percent point, in the last year prior to a major amputation. Similarly,
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43 259 antihypertensive treatments increased from 20% to 64% over the 14 years prior to minor
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45 260 amputations (Figure 2c). The use of beta blocking agents increased from 10% to 41% prior
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47 261 to major amputations and from 8% to 38% prior to minor amputations.

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50 262 The estimated disease progressions, calculated as the combination of the diagnosis
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52 263 prevalence and the medication prevalence, are presented in Figure 3. The progression of
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54 264 diseases prior to a major amputation increased as follows: atherosclerosis^{comb} increased
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56 265 from 5% to 53% during the 14 years, with a 16 percent point increase in the last five years
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3 266 preceding amputation; hypertension^{comb} increased from 23% to 63%; cardiovascular
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5 267 diseases^{comb} increased from 22% to 70%; and diabetes^{comb} increased from 17% to 35%. The
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7 268 use of opioids increased from 10% to 45%, with an 18 percent point increase the last five
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9 269 years prior to amputation. Further, 32% received prescribed opioids three years prior to
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11 270 major amputation (Figure 3a). Among patients with minor amputations, the prevalence of
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13 271 atherosclerosis^{comb} increased from 3% to 51% during the 14 years; cardiovascular
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15 272 diseases^{comb} increased from 16% to 63%; hypertension^{comb} increased from 20% to 66%; and
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17 273 diabetes increased from 29% to 57%. The use of opioids increased from 9% to 34%, with a
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19 274 12 percent point increase in the last five years (Figure 3b).

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23 24 25 276 ***Contacts made to hospitals and GPs during the 14 years prior to amputation***

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27 277 Patients' visits to the healthcare system (hospitals, outpatient clinics, and GPs) during the 14
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29 278 years prior to amputation are presented in Figure 4. 98% of the patients contacted
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31 279 healthcare services at least once during the last year prior to amputation. The proportion of
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33 280 patients that contacted their GPs increased from 85% to 97% during the 14 years prior to
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35 281 amputation. The mean number of visits to GPs each year increased from 4.5 to 7.7 visits per
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37 282 year. The proportion of patients that visited outpatient clinics increased from 25% to 76%,
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39 283 and the mean number of visits to outpatient clinics per year increased from 0.4 to 3.2 visits.
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41 284 The number of hospitalisations increased from 17% to 49%. During the last year prior to
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43 285 amputation, 2% of the patients had no contact with GPs or hospitals, 1% had only contacted
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45 286 hospitals, and 18% had only contacted GPs.

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48 287 Among 851 patients diagnosed with arteriosclerosis without receiving cholesterol-lowering
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50 288 drugs at any time prior to the amputation, 87% had visited their GP, 29% had called out-of-
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52 289 hours care, 47% had been hospitalised, 70% had visited outpatient clinics, and 29% had
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54 290 visited the emergency room during the last year prior to amputation.

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3 292 ***Cumulative incidences of death and re-amputation***
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5 293 Figure 5 shows the cumulative incidences of death and re-amputation for first year after
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7 294 LEA. The hazard ratios for death the first year after an AKA (compared to foot/ankle
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9 295 amputation) were 4.41 (95%CI: 3.44-5.66, $p<0.001$) with no adjustments, 3.39 (95%CI: 2.64-
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11 296 4.37, $p<0.001$) after adjusting for demographics (sex, age, and living conditions), and 4.0
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13 297 (95%CI: 3.09-5.19, $p<0.001$) after also adjusting for co-morbidities (diabetes,
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15 298 arteriosclerosis, hypertension, and use of opioids). The hazard ratios for death the first year
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17 299 after a BKA (compared to foot/ankle amputation) were 2.57 (95%CI: 1.97-3.19, $p<0.001$)
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19 300 without adjustments, 2.28 (95%CI: 1.75-2.97, $p<0.001$) after adjusting for demographics,
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21 301 and 2.39 (95%CI: 1.83-3.13, $p<0.001$) after also adjusting for co-morbidity.
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23

24 302 The hazard ratios for re-amputation the first year after an AKA were 4.16 (95%CI: 3.24-5.34,
25
26 303 $p<0.001$) without adjustments, 3.20 (95%CI: 2.49-4.13, $p<0.001$) after adjusting for
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28 304 demographics, and 3.69 (95%CI: 2.85-4.79, $p<0.001$) after also adjusting for co-morbidity.
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30 305 The hazard ratios for death the first year after a BKA were 2.64 (95%CI: 2.02-3.43, $p<0.001$)
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32 306 without adjustments, 2.34 (95%CI: 1.79-3.05, $p<0.001$) after adjusting for demographics,
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34 307 and 2.4 (95%CI: 1.83-3.14, $p<0.001$) after also adjusting for co-morbidity.
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3 309 **Discussion**
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6 310 This study showed that the prevalence of atherosclerosis was 70% and the prevalence of
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8 311 diabetes was 49% in an unselected national cohort of patients undergoing LEAs. Of the
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10 312 patients with atherosclerosis, 42% had not received cholesterol-lowering treatments,
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12 313 although 87% of these patients had visited their GP at least once during the last year prior to
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14 314 amputation. Additionally, 16% of the patients with diabetes were diagnosed with diabetes the
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16 315 year of the amputation. The majority of patients (85%) had at least one GP contact per year
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18 316 throughout the 14 years prior to amputation, and 64% were in contact with a hospital
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20 317 outpatient clinic three years prior to amputation. Another important finding was that 88% of
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22 318 patients undergoing major extremity amputations had no previous amputations on a lower
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24 319 level. Moreover, only 6% of patients in this cohort had undergone revascularisation prior to
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26 320 amputation. Nevertheless, one out of three patients received prescribed opioids three years
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28 321 prior to amputation.
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31 322 Traditionally, LEA has primarily been associated with long-term complications to diabetes.
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33 323 However, the prevalence of cardiovascular diseases has increased in western countries;
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35 324 consequently, the traditional perceptions must be redefined to identify risk factors for LEA. In
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37 325 our unselected national cohort of patients with major amputations, the majority (83%) was
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39 326 diagnosed with atherosclerosis, and a smaller proportion had diabetes (33%). In
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41 327 comparison, patients with minor amputations had a higher prevalence of diabetes (64%) and
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43 328 lower prevalence of atherosclerosis (53%). Similar distributions were also identified by The
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45 329 Global Lower Extremity Amputation Study Group, 2000 (13). Further, we also found a 28
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47 330 percent point difference between the proportion of patients who received cholesterol-
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49 331 lowering drugs and the proportion of patients diagnosed with atherosclerosis. Also, among
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51 332 patients with diabetes there was a six percent point gap between patients having diabetes
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53 333 and patients receiving anti-diabetic treatment, indicating an unsolved clinical problem in
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55 334 identifying atherosclerosis and diabetes. Indeed, timely treatment might have saved these
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3 335 patients from a extremity amputation. The lack of recognition of symptoms related to PAD
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5 336 among both patients and health care professionals may be related to a lack of knowledge
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7 337 that inhibited patients to react on symptoms and consult their GP in time (26). However, the
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9 338 increased use of prescribed opioids in the years leading up to the amputation could indicate
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11 339 the presence of PAD, all though we have no information on the indication for the
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13 340 prescription. This study supports the conclusion made by Jones et al. that calls for education
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15 341 programs to focus on prevention and early identification to ensure adequate treatment for
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17 342 preventing LEA (5).

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20 343 In this study, few patients had a history of minor amputations performed prior to the major
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22 344 index amputation; 89% and 85% of patients with AKA and BKA, respectively, had no history
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24 345 of previous amputation preceding the first-time major amputations. Heyer et al. reported that
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26 346 92 % of their patients had no previous amputation based on data from health insurance
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28 347 companies (12) and Buckley et al. found that 28% of a selected cohort of patients with
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30 348 diabetes had a history of amputations (16). Further, Currran et al. reported that 61% had a
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32 349 history of either revascularisation or amputation based on data from a surgeon database (3).

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34 350 In this study, only 6% of the patients had received revascularisations (angioplasty or bypass)
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36 351 prior to the index amputation. These results were surprising as revascularisation surgery is
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38 352 still considered one of the central treatment strategies for critical ischaemia in lower
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40 353 extremities (27,28). Similarly, Moxey et al. found a 9% prevalence of revascularisation in an
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42 354 unselected, nationwide cohort (29). However, Ahmad et al. found a 30% prevalence of
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44 355 revascularisation in an unselected population cohort in England (11). Ahmad et al. also
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46 356 demonstrated demographic variations in the prevalence of amputations and
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48 357 revascularisations, which were associated with social inequalities and the presence of
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50 358 chronic diseases in some geographical regions. The finding that one third of patients
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52 359 received intensive pain treatment already three years prior to major amputation indicate
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54 360 symptoms of ischaemia, which appear several years prior to amputation. Thus, it is essential
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56 361 that leg pain should be recognised as a symptom of PAD to ensure that patients are referred
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3 362 to specialists (30). In Denmark, the ankle and toe blood pressures are measured to
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5 363 calculate the Ankle-Brachial index (ABI) (31), a non-invasive diagnostic test for PAD (32).
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7 364 This procedure is mainly performed in hospitals, and rarely by the GP. The majority of
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9 365 patients' maintained regular and increasing contact with their GPs, thus, early identification
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11 366 might be feasible, because patients do seek medical advice in the years prior to the
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13 367 amputation. Furthermore, our results showed that 63% of patients were also in regular
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15 368 contact with outpatient clinics at hospitals already three years before the amputation, and
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17 369 they increasingly (from 32% to 49%) underwent hospitalisation during the last years
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19 370 preceding amputation. Buckley et al. followed patients with diabetes for seven years prior to
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21 371 LEA, and concluded a need for early referral to specialists to reduce risk of LEA (16). Our
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23 372 study found that the majority (76%) of patients visited the out-patient clinic and as such is
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25 373 accessible for early identification. It has been suggested that PAD screening could be
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27 374 performed with non-invasive methods, like the ABI (33); . Other studies have indicated that
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29 375 routine screening could promote preventive treatment, and that a screening strategy could
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31 376 cost-effectively prevent the progression of PAD and cardiovascular events (34,35).
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33 377 Alternatively, Brand (36) and Boulton et al. (37) have suggested that a simple clinical
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35 378 examination of a patient's feet could indicate a need for further test to identify PAD. Thus,
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37 379 treatment could be initiated (including specialist referrals) to prevent ulcers due to ischaemia,
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39 380 and thus, prevent LEA.
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43 381 The present study confirmed that the risk of re-amputation increased after minor
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45 382 amputations, and that the risk of death was highest among patients who required AKAs. In
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47 383 contrast, neither demographics nor comorbidities could explain the low chance of survival.
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49 384 Thus, other factors must affect the outcome after LEA, such as the general health status and
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51 385 the nutritional status of a patient. In addition, factors related to the perioperative treatment,
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53 386 like the delay to surgery, could have a negative impact on the outcome (38). Similar results
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3 387 were reported by Jones et al., Hoffstad et al., and Wiessman et al., who called for more
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5 388 comprehensive, multidisciplinary efforts (5,7,10).
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8 389 The strength of this study was the use of an unselected, nationwide cohort based on the
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10 390 national registry, which maintained information recorded over a period of 14 years prior to
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12 391 the amputation. Furthermore, we could crosslink data in various registries at an individual
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14 392 level, which made it possible to follow patients over time. The main limitation was the lack of
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16 393 a control group. An age-, sex-, and geographically-matched control group could allow
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18 394 differentiation between disease progression due to aging and disease progression that leads
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20 395 to amputation. Furthermore, this type of comparison could also reveal inequalities in
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22 396 healthcare services, as has been shown in other countries (11). An inherent limitation was
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24 397 that the data did not allow an estimation of patient compliance with the prescribed
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26 398 medication. Further, it was not possible to access the diagnosis recorded by the GP, as
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28 399 these data are not included in the national registry nor the indication for the prescribed
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30 400 medication as this has just recently been included in the registry.
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33 401

36 402 **Conclusion**

37
38 403 Atherosclerosis is the primary comorbidity followed by hypertension and diabetes in this
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40 404 unselected cohort of patients undergoing major extremity amputation. In this study, one third
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42 405 of patients with LEA were living with undiagnosed or untreated atherosclerosis and one out
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44 406 of six were living with undiagnosed diabetes despite a regular contact with their GPs and
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46 407 outpatient clinics for several years prior to the amputation. For the majority of patients
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48 408 undergoing major LEAs, the amputation was a first-time amputation. Additionally, only a
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50 409 small number of patients underwent extremity-saving procedures, although one in three had
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52 410 received opioid prescriptions several years before the amputation. The overall findings of
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54 411 this study suggest that the need of opioids, combined with the presence of hypertension,
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56 412 diabetes, or another cardiovascular disease, could be an indication of PAD which is highly
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3 413 associated with lower extremity amputation. Further, clinicians are encouraged to initiate
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5 414 medical treatment supplemented with a careful inspection of the patient's feet as this non-
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7 415 invasive examination may detect an early indication of low circulation.
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10
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12
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14
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25
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29 430 **Consent for publication**

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31 431 Not applicable

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34 432 **Data sharing statement**

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36 433 The datasets supporting the conclusions of this article are available in the Statistics
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38 434 Denmark, <http://www.dst.dk/>. Statistics Denmark managed and provided the secured access
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40 435 In according to Danish regulations, data are available by applying Statistics Denmark.

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43 436 **Author contributors**

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45 437 SJ and JP describe the idea behind the study. PSJ and OA applied for funding to the study.
46
47 438 PSJ, JP, KKM, IP and OA signed the study. PSJ and JP applied for data at Statistics
48
49 439 Denmark. PSJ and JP provided the statistical expertise. IP, KKM and OA provided the
50
51 440 clinical and medical expertise. PSJ and JP performed the data management and analysis.
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53 441 All authors helped interpret the data. The accuracy of data and analysis was reviewing by all
54
55 442 authors who can take responsibility for the integrity of the data and the accuracy of the data

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3 443 analysis. PSJ drafted the manuscript. All authors reviewed and critically revised the
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5 444 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
		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 status¹				
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)	999 (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. ¹Missing n=12. ²Married or residing with a partner. ³All ICD10 diagnoses. ⁴ACTcodes for main groups

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

	Major amputations			Minor amputations	
	Total, N (%)	Above Knee	Below Knee	Total, N (%)	P value*
		n (%)	n (%)		
	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

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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	Below Knee	Total, N (%)	P value*
		n (%)	n (%)		
	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

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3 561 **Figures titles and legends**

4 562
5 563 **Figure 1**

6 564
7 565 Title: Figure 1. Flowchart shows study selection of patients with lower extremity amputations
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9 566 between 01.01.2010 -31.12.2011 in Denmark

10
11 567 Legends: (1) Excluded due to previous amputation define as amputation on the same level
12
13 568 or bilateral amputation on a higher level than the index amputation in 2010-11; (2) include
14
15 569 hip-exarticulation; (3) include knee disarticulation.

16
17 570
18 571 **Figure 2**

19 572
20 573 Title: Figure 2. The prevalence of comorbidities and prescribed medications during the 14
21
22 574 years preceding major and minor lower extremity amputations.

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24 575 **Figure 3**

25 576
26 577 Title: Figure 3. 14 years of estimated progression of chronic diseases preceding (a) major
27
28 578 and (b) minor lower extremity amputations.

29
30 579 Legends: The prevalence of comorbidities, defined by both ICD-10 coding and the use of
31
32 580 prescribed medications (ACT code), was estimated each year.

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34 581
35 582 **Figure 4**

36
37 583 Title: Figure 4. Contacts with the healthcare system during the 14 years preceding lower
38
39 584 extremity amputation. Patients are grouped according to (a) major amputations, and (b)
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41 585 minor amputations

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43 586 **Figure 5**

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45 587 Title: Figure 5. One-year cumulative outcomes. The cumulative probabilities of (*left*) re-
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47 588 amputation procedures and (*right*) survival are shown for patients that received major (AKA
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49 589 and BKA) and minor lower extremity amputations

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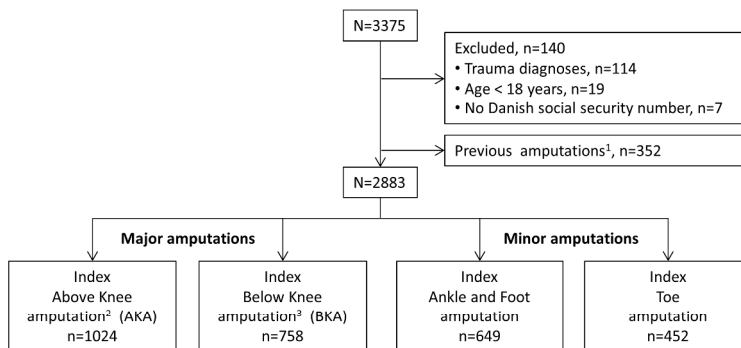


Figure 1. Flowchart shows study selection of patients with lower extremity amputations between 01.01.2010 -31.12.2011 in Denmark

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)

only

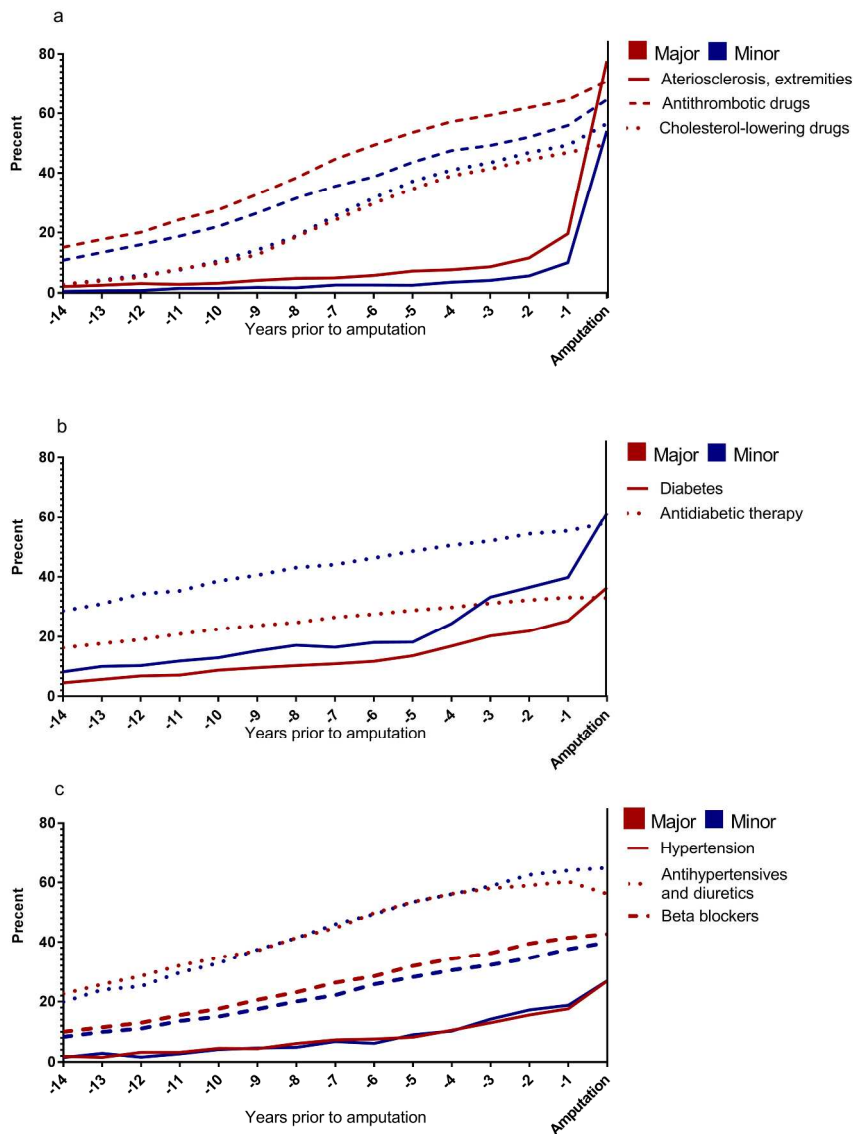


Figure 2. The prevalence of comorbidities and prescribed medications during the 14 years preceding major and minor lower extremity amputations.

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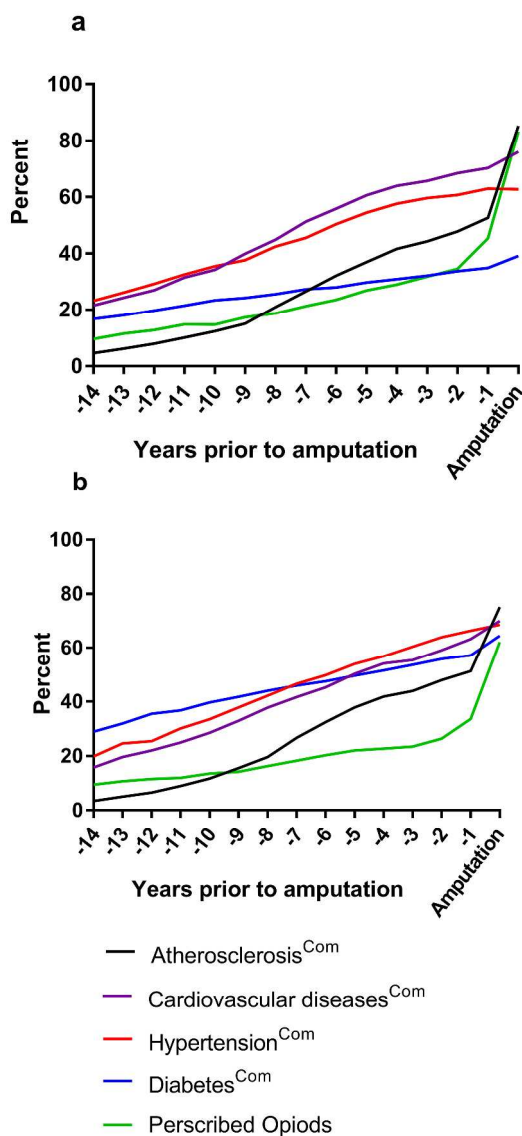


Figure 3. 14 years of estimated progression of chronic diseases preceding (a) major and (b) minor lower extremity amputations. The prevalence of comorbidities, defined by both ICD-10 coding and the use of prescribed medications (ACT code), was estimated each year.

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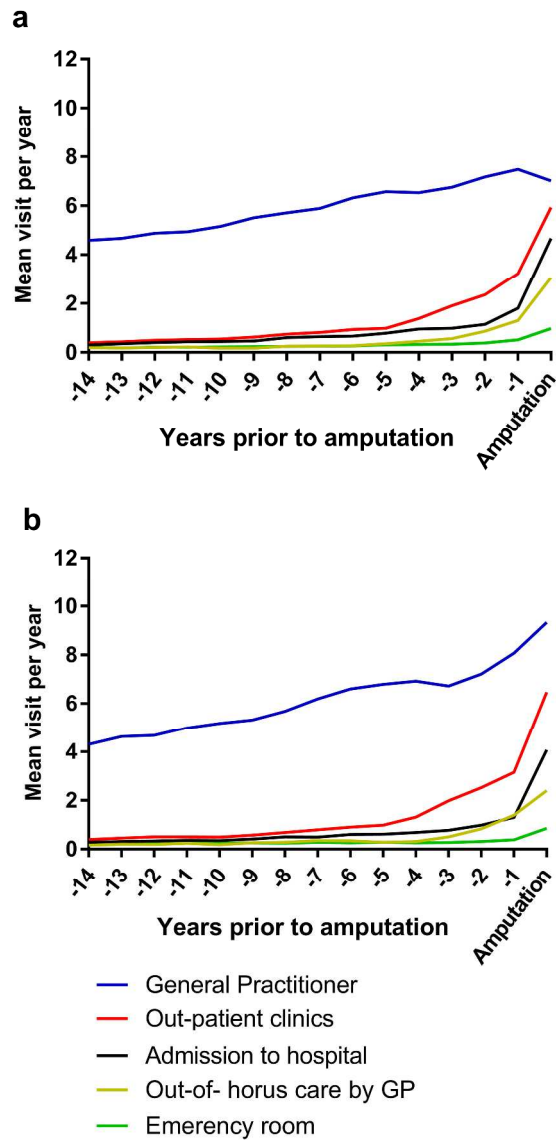
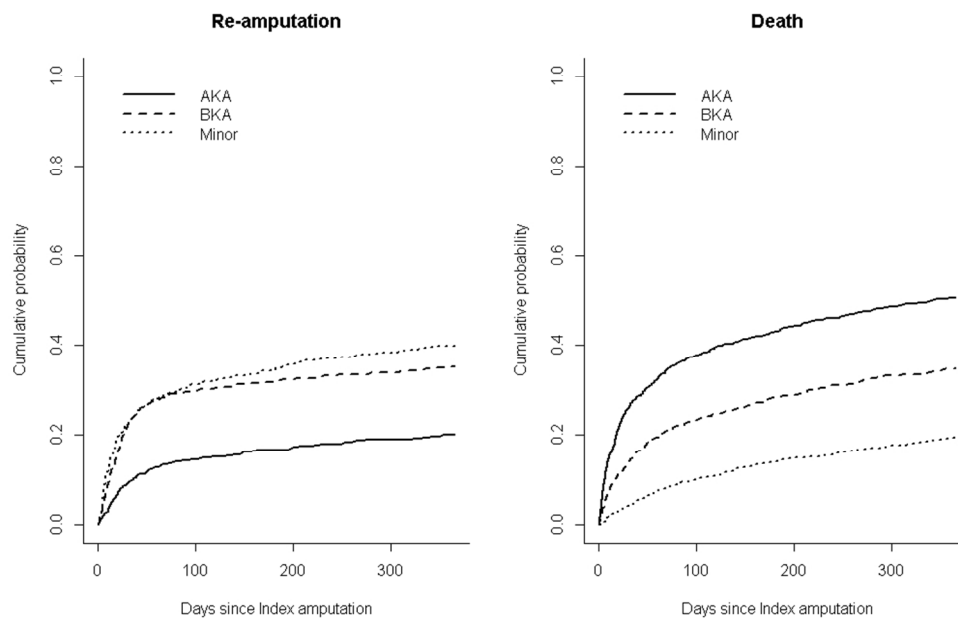


Figure 4. Contacts with the healthcare system during the 14 years preceding lower extremity amputation. Patients are grouped according to (a) major amputations, and (b) minor amputations

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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)

ew only

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	DI97, DL88, DI89, 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
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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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Page 12, (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	Page 12, (Table1)
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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 15 Tabel 1
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:	<i>BMJ Open</i>
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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, Health care service

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Manuscripts

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2
3 1 **Title**

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6 2 Progression of disease preceding lower extremity amputation in Denmark: A longitudinal
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8 3 registry study of diagnoses, use of medication and healthcare services 14 years prior to
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10 4 amputation

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56
57 29 **Word count:** 3980

1
2
3 30 **Abstract**
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5

6 31 **Objectives:** Patients with non-traumatic lower extremity amputation are characterised by
7
8 32 high age, multi-morbidity and polypharmacy and long-term complications of atherosclerosis
9
10 33 and diabetes. To ensure early identification of patients at risk of amputation, we need to gain
11
12 34 knowledge about the progression of diseases related to lower extremity amputations during
13
14 35 the years preceding the amputation.
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16
17 36 **Design:** A retrospective population-based national registry study.
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19
20 37 **Setting:** The study includes data on demographics, diagnoses, surgery, medications, and
21
22 38 healthcare services from five national registries. Data were retrieved from 14 years before
23
24 39 until 1 year after the amputation. Descriptive statistics were used to describe the progression
25
26 40 of diseases and use of medication and healthcare services.
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28
29 41 **Participants:** An unselected cohort of patients (≥ 50 yrs; $n=2883$) subjected to a primary
30
31 42 non-traumatic lower extremity amputation in 2010 or 2011 in Denmark.
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33 43 **Results:** The prevalence of atherosclerosis, hypertension and diabetes was 70%, 53% and
34
35 44 49%, respectively. Among of patients with atherosclerosis, 42 % had not received
36
37 45 cholesterol-lowering treatment even though 87% had visited their general practitioner within
38
39 46 the last year prior to amputation. Further, 16% were diagnosed with diabetes at the time of
40
41 47 the amputation. The prevalence of cardiovascular diseases increased from 22% to 70%,
42
43 48 atherosclerosis from 5% to 53%, and diabetes from 17% to 35% over the 14 years preceding
44
45 49 major amputation. Of all patients, 64% had been in contact with the hospital or out-patient
46
47 50 clinics within the last three years and 29% received a prescription of opioids three years prior
48
49 51 to the amputation.
50

51
52 52 **Conclusion:** Among patients with non-traumatic lower extremity amputation, one-third live
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54 53 with undiagnosed and untreated atherosclerosis and one-sixth suffer from undiagnosed
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56 54 diabetes despite continuous contacts to general practitioner and the hospital. This study
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3 55 emphasises a need for enhanced focus, among both hospital clinicians and general
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5 56 practitioners, on the early identification of atherosclerosis and diabetes.
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7

8 57 **Keywords** Lower extremity amputation, Atherosclerosis, Diabetes, Healthcare services
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11 58 **Strengths and limitations of the study**
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- 14
15 59 • The strengths of this national registry study were the inclusion of data describing
16
17 60 diagnoses and use of medication and healthcare services during the last 14 years
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19 61 preceding non-traumatic LEA performed in Denmark.
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21
22 62 • The main limitation was the lack of a control group. An age-, sex-, and geographically-
23
24 63 matched control group would have allowed differentiation between disease progression
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26 64 due to aging and disease progression leading to amputation. An inherent limitation was
27
28 65 that the data did not allow an estimation of patient compliance with the prescribed
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30 66 medication.
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32

33 67 **Abbreviations**
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36 68 LEA: lower extremities amputation
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38 69 Major LEA: Lower extremity amputation performed above the ankle level
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40 70 Minor LEA: Lower extremity amputation performed below the ankle level
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42 71 AKA: Above knee amputation
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44 72 BKA: Below knee amputation
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46 73 PAD: Peripheral artery disease
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48 74 GP: General practitioner
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75 Introduction

76 Lower extremity amputation (LEA) is a severe event associated with loss of mobility, pain,
77 decreased quality of life, major disfigurement, and increased risk of re-amputation and
78 hospitalisation (1–3). Even though the worldwide incidence of LEA has declined over the last
79 two decades, significant variations persist; from 5.8 to 31 per 10⁵ individuals in different
80 populations (4). The reported one-year mortality rate was 12% to 58% (5–8), with the highest
81 mortality rate (45%–58%) associated with above-the-knee amputations (AKA) (9,10). Age
82 and the severity of comorbidities are the most prominent prognostic factors for mortality after
83 LEA (6,7).

84 The most prevalent comorbidities in patients with LEA are atherosclerosis primary as
85 periphery vascular disease (PAD) and diabetes (4,11–13). Studies have reported the
86 prevalence's of diabetes to be between 52%–64% (3,5,14) and approximately 80% of the
87 patients with LEA are either diagnosed with diabetes or PAD (12). In a cohort of patients with
88 diabetes, 18% had a cardiovascular disease with PAD being most prevalent (15). Among
89 patients diagnosed with both diabetes and PAD, the risk of amputation is 1.5 times higher
90 than in patients diagnosed with PAD alone and five times higher than in patients only
91 diagnosed with diabetes (13). The global prevalence of diabetes and PAD among patients
92 with LEA varies among populations due to ethnicity and socioeconomic e.g. (4,16).

93 Currently, the global prevalence of diabetes is estimated to 9% of which 90% is
94 characterised as type 2 diabetes (17) and is expected to continue to increase over the next
95 twenty years to 10%. During the last decade, the global prevalence of PAD has increased by
96 23%, with the highest increase among low-income countries (18). The risk factors for PAD
97 are age, smoking, diabetes, hypertension, dyslipidaemia, and obesity (19). The NICE
98 guidelines for lower limb peripheral arterial disease state that there is substantial evidence
99 establishing benefits for lowering cholesterol drugs for patients with PAD and the use of
100 limb-saving procedure are also recommended (20). The benefits of cholesterol lowering
101 drugs have shown a significant reduction in the risk of major amputation (21,22).

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3 102 To our knowledge, only a few studies have previously investigated the progression of
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5 103 diseases and use of health-care services before amputation using historical longitudinal
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7 104 data. One case-control study including data collected seven years before amputation and
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9 105 recommended early referral to a medical specialist to prevent LEA among patients with
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11 106 diabetes (23), all though a population-based study found that repeated visit to the hospital
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13 107 did not lower the risk of amputation among patients with diabetes/PAD (24). Other studies
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15 108 have also shown delayed referral to revascularization to prevent loss of extremity and
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17 109 inadequate treatment of cholesterol-lowering drug (25,26)
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19
20 110 Nevertheless, the risk of amputation remains high, and some patients remain undiagnosed
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22 111 until it is too late to prevent LEA (27). The first step to improving the early identification is to
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24 112 acquire more knowledge of the characteristics of patients, variation and progression of
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26 113 diseases and use of health care services prior to amputations. The aim of this study was to
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28 114 explore the progression of LEA-related diseases. We examined the use of medication and
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30 115 the number of contacts with health care services during the 14 years leading up to LEA,
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32 116 among all Danish patients that underwent LEAs in 2010 or 2011. Finally, we studied the
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34 117 associations between LEA-related diseases and the one-year prognosis after the LEA
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3 119 **Methods**
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6 120 **Setting**
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8 121 The Danish healthcare system is tax-funded and offers free and equal access to medical
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10 122 care. All citizens have a general practitioner (GP) who provides referrals to specialists and
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12 123 hospital treatments. The GPs are responsible for their patients' medical treatment.
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14 124 Prescribed medications and other healthcare services, such as a physiotherapy, etc., are
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16 125 partly tax-funded, with a differential out-of-pocket fee.
17

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19 126 **Study design and data sources**
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21
22 127 We included data from the following five national registries: (1) The National Patient Registry
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24 128 (NPR), which contains information on hospitalisations, including visits to outpatient clinics
25
26 129 and emergency rooms (28), surgical procedures, coded according to the Nordic
27
28 130 Classification of Surgical Procedures (NCSP), and diagnoses coded according to the
29
30 131 International Classification of Diseases (ICD-10); (2) The National Prescription Registry,
31
32 132 which contains information on prescribed medications picked up at the pharmacy (29), the
33
34 133 data are coded according to the global Anatomical Therapeutic Chemical (ATC)
35
36 134 classification system; (3) The Danish National Health Service Registry for Primary Care
37
38 135 (NHSR), which contains information on all contacts with GPs, including out-of-hours care
39
40 136 from GPs and practising medical specialists (30); (4) The Danish Civil Registration System
41
42 137 (CRS), which contains information on gender, date of birth, vital status, spouses and
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44 138 residents (31); and (5) The Attainment Registry, which contains data on education level. All
45
46 139 Danish citizens are registered with a unique personal identification number (CPR number),
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48 140 which allows linkage with all national registries at an individual level. Statistics Denmark
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50 141 provided the data (<http://www.danmarksstatistik.dk/en>).
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3 142 **Study cohort**
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5 143 We included patients with at least one of the following surgical procedures, performed
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7 144 between the 1st of January 2010 and 31st of December 2011: Hip-exarticulation or trans-
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9 145 femoral amputation (i.e., Above-knee amputation [AKA]); knee disarticulation or trans-tibial
10
11 146 amputation (i.e., Below-the-knee amputation [BKA]); foot amputation; or toe amputation. See
12
13 147 supplementary materials for detailed information. To eliminate trauma-related amputations,
14
15 148 we excluded patients with a trauma diagnosis recorded at any time prior to the amputation.
16
17 149 We also excluded foreign patients without a CPR number or below 18 years of age. To
18
19 150 ensure homogeneity within the groups, we defined an index amputation as the first surgical
20
21 151 amputation performed as an AKA, BKA, foot- or toe amputation in 2010 and 2011.
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24 152 **Categorisation of amputation procedures**
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26
27 153 For patients who received more than one amputation procedure on the same day, the most
28
29 154 severe (proximal) procedure was identified for analysis. The severity of different types of
30
31 155 amputations (based on surgical codes) was ranked from the most severe procedure as hip-
32
33 156 exarticulation and transfemoral amputation to the least severe as a toe amputation
34
35 157 procedure. A detailed description is present in the supplementary material. When patients
36
37 158 had both a left- and right-side amputation code on the same day, the procedure was
38
39 159 categorised as a bilateral amputation. AKA and BKA were classified as major amputations,
40
41 160 and foot or toe amputations were classified as minor amputations.
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44 161 **Demographics, comorbidities, medications, and contacts with healthcare services**
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46 162 For each patient, we retrieved cumulative registry information on the education level, living
47
48 163 conditions, socioeconomic status, place of residence, diagnoses, prescribed medications,
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50 164 contacts with healthcare services, re-amputations, and death, which had been recorded
51
52 165 between 01.01.1997 and 31.12.2012. The Elixhauser Comorbidity Index was used to identify
53
54 166 the progression of comorbidities over the 14 years prior to amputation. The Index includes
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56 167 31 pre-defined comorbidities; however, in this study, we combined the pre-defined codes for
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3 168 uncomplicated and complicated diabetes and hypertension (32). The Elixhauser Comorbidity
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5 169 Index was supplemented with ICD-10 codes for atherosclerosis, including atherosclerosis in
6
7 170 the lower extremities, diabetic neuropathy, retinopathy, nephropathy foot ulcer, other ulcers
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9 171 (not related to diabetes), stroke, emboli, bone cancer, and arthrosis, see supplementary
10
11 172 material. The severity of the comorbidity identified at the time of the index amputation was
12
13 173 evaluated with the Charlson Comorbidity Index (33). We divided the patients into three
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15 174 groups, according to the Charlson Comorbidity Index: 0-1, 2, and 3+, where a higher score
16
17 175 predicted an increased risk of mortality. The prescribed medications were defined as
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19 176 medications that were picked up from the pharmacy at least once each year. The prescribed
20
21 177 medications were grouped according to ACT codes. The coding and the classifications of
22
23 178 drugs were defined by the authors and validated by consensus agreement among three
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25 179 pharmacists who did not participate in the study, see supplementary material.
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28 180 The NPR registry contains only information on diagnoses recorded during hospitalisation,
29
30 181 and not by GPs. Therefore, central diseases were defined by combining the prevalence of
31
32 182 the medication (ACT- codes) collected from the pharmacy with the registered diagnosis
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34 183 (ICD-10 codes) from hospitals: diabetes^{comb}, atherosclerosis^{comb}, cardiovascular diseases^{comb}
35
36 184 and hypertension^{comb} (see supplementary material). A visit to a GP was defined as a show-
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38 185 up at the GP clinic, visits to outpatient clinics included only clinics at the hospitals while a
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40 186 visit to a medical specialist only includes private clinics.
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43 44 187 **Ethical approval**

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46 188 This register-based study included only anonymous data from national registries and had no
47
48 189 patient contact. The scientific board of Statistics Denmark and "Statens Serum Institut"
49
50 190 approved the study (project no 704122).
51

52 53 191 **Statistics**

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55 192 Descriptive data, comorbidities, and the use of medication for each of the amputation groups
56
57 193 were expressed as frequencies with percentages, for categorical data, or as median and
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3 194 intraquartile range (IQR = 25th to 75th percentile) for continuous data. A comparison
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5 195 between major and minor amputations was made with a χ^2 test, for categorical data, and a
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7 196 Kruskal-Wallis test for continuous data. Diagnoses and relevant medications were compared
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9 197 between amputation types and atherosclerosis, diabetes, hypertension and between
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11 198 cardiovascular disease (CVD), diabetes and patients without. The prevalence of diagnoses
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13 199 and use of medications over time are depicted as graphs of the proportions of patients with a
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15 200 given disease, and the proportion that used a given medication, respectively. The difference
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17 201 in prevalence over time is expressed as percent point (pp). The data analysis was performed
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19 202 with SAS 9.4, and the cumulative incidence plots were constructed with R 3.2.2. Graphs of
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21 203 the progression over time were created with GraphPad Prism 6.07, and the flowchart was
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23 204 created in PowerPoint 2010. P-values less than 5% were considered significant.

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3 207 **Results**
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6 208 A total of 3375 patients underwent an LEA in Denmark during 2010 and 2011. Of these, 4%
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8 209 required LEAs due to trauma, and were excluded from the cohort (Figure 1). Additionally,
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10 210 352 patients (11%) were excluded, due to a previous amputation on the same or opposite
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12 211 leg, at the same or a higher level, leaving 2883 patients who fulfilled the criteria for
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14 212 undergoing an index amputation during 2010 and 2011. Major amputations were performed
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16 213 in 1782 patients (62%), and minor amputations were performed in 1101 patients (38%).
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18 214 Patient characteristics are presented in Table 1. Among patients with major amputations,
19
20 215 1562 (88%) had not received previous amputations. Among the 266 patients with previous
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22 216 amputations (on a lower level), 101 patients (38%) were bilaterally amputated.
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25 217 ***Comorbidities and medical treatment in the year of amputation***
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28 218 Patient diagnoses and current medications that were recorded at the time of the index
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30 219 amputation are presented in Table 2 and 3. Both diabetes and atherosclerosis were
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32 220 diagnosed in 32% of patients (577/1782) with major amputations and 35% of patients
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34 221 (382/1101) with minor amputations. A subgroup analysis of characteristics, comorbidities
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36 222 and medical treatment among patients diagnosed with either CVD including arteriosclerosis,
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38 223 diabetes or neither are presented in Table 4. A total of 2350 (82%) patients were diagnosed
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40 224 with CVD of which 1185 had CVD without diabetes and 1451 patients were diagnosed with
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42 225 diabetes of which 286 were not diagnosed with CVD. Furthermore, among patients
43
44 226 diagnosed with atherosclerosis, 42% (851/2017) had not received cholesterol-lowering drugs
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46 227 at the time of amputation. The absence of cholesterol-lowering treatment was observed
47
48 228 significantly more among patients with major amputations than among those with minor
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50 229 amputations, (46% (650/1428) vs 34% (201/589); $p < 0.001$). Among patients diagnosed with
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52 230 cardiovascular diseases (CVD) and patients diagnosed with diabetes, had 46% (543/1185)
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54 231 and 65% (940/1451) received cholesterol-lowering before the amputation, see Table 4.
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56 232 Among patients diagnosed with diabetes, 225 patients (16%) did not at any time receive
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3 233 insulin or blood glucose-lowering drugs preceding the amputation. The absence of
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5 234 antidiabetic treatment prior to the amputation was observed significantly more often among
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7 235 patients with major amputations than among patients with minor amputations (19%
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9 236 (134/697) vs 13% (91/710), $p < .001$).

10
11 237 ***Disease progression and medications during the 14 years prior to amputation***

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14 238 Figure 2 shows the gradual increases in the proportion of patients with the most common
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16 239 diagnoses (atherosclerosis, diabetes, and hypertension) recorded during hospitalisations
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18 240 and the medications used (including antithrombotic agents, cholesterol-lowering treatments,
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20 241 antidiabetic drugs, and antihypertensive therapies) during the 14 years prior to the
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22 242 amputation. Among patients undergoing major amputations, the prevalence of
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24 243 atherosclerosis increased from 2% to 20% over the first 13 years, and a 58 pp increase was
25
26 244 observed during the last year preceding the amputation. During the 14 years, the use of
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28 245 cholesterol-lowering drugs increased from 3% to 50%. There was a 28 pp difference
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30 246 between patients diagnosed with atherosclerosis who received cholesterol-lowering
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32 247 treatment or not prior to the amputation. Furthermore, the use of antithrombotic drugs
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34 248 increased from 15% to 65% during the first 13 years, and the use further increased by 6
35
36 249 percent point in the last year (Figure 2a). Among patients with minor amputations, the
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38 250 prevalence of diabetes increased from 8% to 40%, and antidiabetic treatments increased
39
40 251 from 29% to 55%. During the last year, the prevalence of diabetes increased by 21 percent
41
42 252 point, and the gap between treatment and diagnosis was only 3 percent point prior to minor
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44 253 amputation (Figure 2b). Antihypertensive treatments increased from 23% to 60% during the
45
46 254 first 13 years, and then dropped slightly, by 4 percent point, in the last year prior to a major
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48 255 amputation. Similarly, antihypertensive treatments increased from 20% to 64% over the 14
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50 256 years prior to minor amputations (Figure 2c).

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54 257 The estimated disease progressions, calculated as the combination of the diagnosis
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56 258 prevalence and the medication prevalence, are presented in Figure 3. The progression of
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3 259 diseases prior to a major amputation increased as follows: atherosclerosis^{comb} increased
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5 260 from 5% to 53% during the 14 years, with a 16 percent point increase in the last five years
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7 261 preceding amputation; hypertension^{comb} increased from 23% to 63%; cardiovascular
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9 262 diseases^{comb} increased from 22% to 70%; and diabetes^{comb} increased from 17% to 35%. The
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11 263 use of opioids increased from 10% to 45%, with an 18 percent point increase the last five
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13 264 years prior to amputation. Further, 32% received prescribed opioids three years prior to
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15 265 major amputation (Figure 3a). Among patients with minor amputations, the prevalence of
16
17 266 atherosclerosis^{comb} increased from 3% to 51% during the 14 years; cardiovascular
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19 267 diseases^{comb} increased from 16% to 63%; hypertension^{comb} increased from 20% to 66%; and
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21 268 diabetes increased from 29% to 57%. The use of opioids increased from 9% to 34%, with a
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23 269 12 percent point increase in the last five years (Figure 3b). In total, 29 % received opioids
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25 270 three years before the amputation.

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

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

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

285 ***Cumulative incidences of death and re-amputation***

286 Figure 4 shows the cumulative incidences of death and re-amputation for first year after
287 LEA. The hazard ratios for death the first year after an AKA (compared to foot amputation)
288 were 4.41 (95%CI: 3.44-5.66, $p<0.001$) with no adjustments, 3.39 (95%CI: 2.64-4.37,
289 $p<0.001$) after adjusting for demographics (gender, age, social status and living
290 arrangement), and 4.0 (95%CI: 3.09-5.19, $p<0.001$) after also adjusting for co-morbidities
291 (diabetes, arteriosclerosis, hypertension, and use of opioids). The hazard ratios for death the
292 first year after a BKA (compared to foot amputation) were 2.57 (95%CI: 1.97-3.19, $p<0.001$)
293 without adjustments, 2.28 (95%CI: 1.75-2.97, $p<0.001$) after adjusting for demographics,
294 and 2.39 (95%CI: 1.83-3.13, $p<0.001$) after also adjusting for co-morbidity.

295 The hazard ratios for re-amputation the first year after an AKA were 4.16 (95%CI: 3.24-5.34,
296 $p<0.001$) without adjustments, 3.20 (95%CI: 2.49-4.13, $p<0.001$) after adjusting for
297 demographics, and 3.69 (95%CI: 2.85-4.79, $p<0.001$) after also adjusting for co-morbidity.

298 The hazard ratios for death the first year after a BKA were 2.64 (95%CI: 2.02-3.43, $p<0.001$)
299 without adjustments, 2.34 (95%CI: 1.79-3.05, $p<0.001$) after adjusting for demographics,
300 and 2.4 (95%CI: 1.83-3.14, $p<0.001$) after also adjusting for co-morbidity.

301 **Discussion**

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

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3 311 this cohort had undergone revascularisation prior to amputation. Nevertheless, one out of
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5 312 three patients received prescribed opioids three years prior to amputation. Traditionally, LEA
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7 313 has been associated with long-term complications of diabetes. However, the prevalence of
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9 314 cardiovascular diseases are increasing in western countries; consequently, the traditional
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11 315 perceptions must be redefined to identify risk factors for LEA. In our national cohort of
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13 316 patients with major amputations, the majority (83%) was diagnosed with atherosclerosis, and
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15 317 less (33%) had diabetes. In comparison, patients with minor amputations had a higher
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17 318 prevalence of diabetes (64%) and lower prevalence of atherosclerosis (53%). Similar
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19 319 distributions were identified by The Global Lower Extremity Amputation Study Group, 2000
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21 320 (16).

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24 321 According to the guidelines, our results indicate a suboptimal treatment of atherosclerosis
25
26 322 and identification of diabetes. There was a 28 percent point difference between the
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28 323 proportion of patients who received cholesterol-lowering drugs and the proportion of patients
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30 324 diagnosed with atherosclerosis. Also, among patients with diabetes, there was a six percent
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32 325 point gap between patients having diabetes and patients receiving anti-diabetic treatment,
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34 326 indicating an unsolved clinical problem in identifying atherosclerosis and diabetes. Indeed,
35
36 327 timely treatment might have saved these patients from an extremity amputation. The lack of
37
38 328 recognition of symptoms related to PAD among both patients and health care professionals
39
40 329 may be linked to a lack of knowledge inhibiting patients to react on symptoms and consult
41
42 330 their GP in time (34). Additionally, only 6% of the patients had received revascularisations
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44 331 (angioplasty or bypass) prior to the index amputation. These results were concerning as
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46 332 revascularisation surgery still is an essential part of the treatment for critical ischaemia in
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48 333 lower extremities (35,36). Similarly, Moxey et al. also found a low prevalence of
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50 334 revascularisation of 9% in an unselected, nationwide cohort (37). However, Ahmad et al.
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52 335 found a 30% prevalence of revascularisation in an unselected population cohort in England
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54 336 (11). Ahmad et al. also demonstrated demographic variations in the prevalence of
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3 337 amputations and revascularisations, which were associated with social inequalities and the
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5 338 presence of chronic diseases.
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8 339 The results of this study point towards several possibilities for preventing LEA. The finding
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10 340 that 29% of the patients received intensive pain treatment already three years prior to major
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12 341 amputation indicate symptoms of critical extremity ischaemia. For comparison, 2.6 % of the
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14 342 Danish population collected prescribed opioids in 2011 (38). Thus, it is essential that distal
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16 343 lower extremity pain should be recognised as a symptom of PAD to ensure that patients are
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18 344 referred to specialists to confirm the diagnosis (39,40). In Denmark, ankle and toe blood
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20 345 pressure are measured to calculate the Ankle-Brachial Index (ABI) (41), a non-invasive
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22 346 diagnostic test for PAD (42). This procedure is mainly performed at the hospitals, and rarely
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24 347 by the GP. Throughout the 14 years preceding amputation, the majority of patients in this
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26 348 study had regular and increasing contact with their GPs (prevalence increase from 85% to
27
28 349 97%). Thus, early identification might be feasible because patients do seek medical advice in
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30 350 the years prior to amputation. Furthermore, the proportion of patients in contact with
31
32 351 outpatient clinics or were admitted to hospital increased from 25% and 76% and from from
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34 352 32% to 49% during the 14 years preceding the amputation. Buckley et al. followed patients
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36 353 with diabetes for seven years prior to LEA and concluded a need for early referral to
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38 354 specialists to reduce the risk of LEA (23). It has been suggested that PAD screening could
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40 355 be performed with non-invasive methods like the ABI (43). Other studies have indicated that
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42 356 routine screening could promote preventive treatment and that a screening strategy could
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44 357 cost-effectively prevent the progression of PAD and cardiovascular events (44,45).
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47 358 Alternatively, Brand (46) and Boulton et al. (47) have suggested that a simple clinical
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49 359 examination of a patient's feet could indicate a need to confirm PAD. Thus, treatment could
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51 360 be initiated (including specialist referrals) to prevent ulcers due to ischaemia, and thus,
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53 361 prevent LEA. This study supports the conclusion made by Jones et al. that calls for
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3 362 education programs to focus on prevention and early identification to ensure adequate
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5 363 treatment for preventing LEA (5).
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8 364 In this study, the majority of patients (92%) had no history of previous amputation preceding
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10 365 the index major amputation. Heyer et al. reported that 92 % of their patients had no previous
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12 366 amputation based on data from health insurance companies (12) and Buckley et al. found
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14 367 that 28% of a selected cohort of patients with diabetes had a history of amputations (23).
15

16 368 The present study confirms that the risk of death is highest among patients with major
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18 369 amputation. In contrast, neither demographics nor comorbidities could explain the high risk
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20 370 of death. Thus, other factors must affect the outcome after LEA, such as the general health
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22 371 status and the nutritional status of a patient. Also, factors related to the perioperative
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24 372 treatment, like a delay to surgery, could have a negative impact on the outcome (48). Similar
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26 373 results were reported by Jones et al., Hoffstad et al., and Wiessman et al., who called for
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28 374 more comprehensive, multidisciplinary efforts (5,7,10).
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31 375 The strength of this study was the use of a national cohort based on the national registry,
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33 376 which contained information recorded over a period of 14 years before the amputation.
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35 377 Furthermore, we could crosslink data in various registries at an individual level, which made
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37 378 it possible to follow patients over time. The main limitation was the lack of a control group.
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39 379 An age-, sex-, and geographically-matched control group could allow differentiation between
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41 380 disease progression due to ageing and disease progression that leads to amputation. An
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43 381 inherent limitation was that the data did not allow for an estimation of patient compliance with
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45 382 the prescribed medication. Further, it was not possible to access neither the diagnosis
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47 383 recorded by the GP, as these data are not included in the national registry, nor the indication
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49 384 for the prescribed medication as this has just recently been included in the registry. Finally,
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51 385 data on examinations such as ABI prior to the amputation would have provided a more
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53 386 comprehensive overview of the limb-saving procedure.
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3 387 **Conclusion**
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5 388 In this study, one third of patients with LEA were living with undiagnosed or untreated
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7 389 atherosclerosis and one out of six were living with undiagnosed diabetes despite a regular
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9 390 contact with their GPs and outpatient clinics for several years prior to the amputation. For the
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11 391 majority of patients undergoing major LEAs, the amputation was a first-time amputation.
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13 392 Additionally, only a small number of patients underwent extremity-saving procedures,
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15 393 although one in three had received opioid prescriptions several years before the amputation.
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17 394 The overall findings of this study suggest that the need for opioids, combined with the
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19 395 presence of hypertension, diabetes, or another cardiovascular disease, could be an
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21 396 indication of PAD which is highly associated with lower extremity amputation. Further,
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23 397 clinicians are encouraged to initiate medical treatment supplemented with a careful
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25 398 inspection of the patient's feet as this non-invasive examination may detect an early
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27 399 indication of low circulation.
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8
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10
11 406 **Competing interest**

12
13 407 We have read and understood BMJ policy on declaration of interests and declare that we
14
15 408 have no competing interests

16
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25
26 413 writing the manuscript.

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29 414 **Consent for publication**

30
31 415 Not applicable

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33 416 **Data sharing statement**

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35 417 The datasets supporting the conclusions of this article are available in the Statistics
36
37 418 Denmark, <http://www.dst.dk/>. Statistics Denmark managed and provided the secured access
38
39 419 In according to Danish regulations, data are available by applying Statistics Denmark.

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41
42 420 **Author contributors**

43
44 421 SJ and JP describe the study. PSJ and OA ensured funding. PSJ, JP, KKM, IP and OA
45
46 422 designed the study. PSJ and JP applied for data at Statistics Denmark. PSJ and JP provided
47
48 423 the statistical expertise. IP, KKM and OA provided the clinical and medical expertise. PSJ
49
50 424 and JP performed the data management and analysis. All authors helped interpret the data.
51
52 425 The accuracy of data and analysis was reviewed by all authors who can take responsibility
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54 426 for the integrity of the data and the accuracy of the data analysis. PSJ drafted the
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427 manuscript. All authors reviewed and critically revised the manuscript for intellectual content
428 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
		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 status¹				
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)	999 (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. ¹Missing n=12. ²Married or residing with a partner. ³All ICD10 diagnoses. ⁴ACTcodes for main groups

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

	Major amputations			Minor amputations	
	Total, N (%)	Above Knee	Below Knee	Total, N (%)	P value*
		n (%)	n (%)		
	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

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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	Below Knee	Total, N (%)	P value*
		n (%)	n (%)		
	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

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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		P value*
	N=2636	Cardiovascular disease (CVD) N=1185(%)	Diabetes 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.

¹P 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.

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3 575 **Figures titles and legends**

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5 577 **Figure 1**

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7 579 Title: Figure 1. Flowchart shows study selection of patients with lower extremity amputations
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9 580 between 01.01.2010 -31.12.2011 in Denmark

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11 581 Legends: (1) Excluded due to previous amputation define as amputation on the same level
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13 582 or bilateral amputation on a higher level than the index amputation in 2010-11; (2) include
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15 583 hip-exarticulation; (3) include knee disarticulation.

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18 585 **Figure 2**

19 586
20 587 Title: Figure 2. The prevalence of comorbidities and prescribed medications during the 14
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22 588 years preceding major and minor lower extremity amputations.

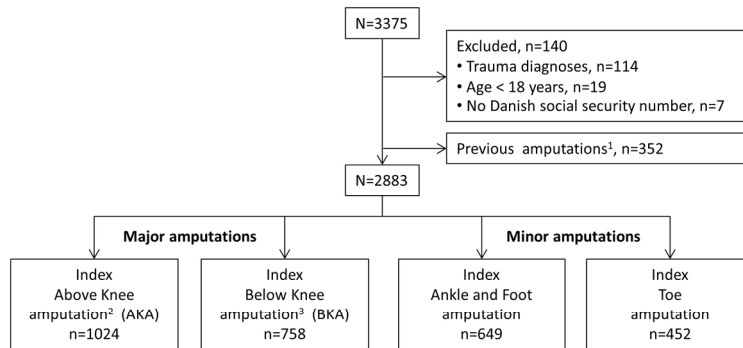
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24 589 **Figure 3**

25 590
26 591 Title: Figure 3. 14 years of estimated progression of chronic diseases and contacts to
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28 592 healthcare system preceding (a,c) major and (b,d) minor lower extremity amputations
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30 593 Legends: The prevalence of comorbidities, defined by both ICD-10 coding and the use of
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32 594 prescribed medications (ACT code), was estimated each year.

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35 596 **Figure 4**

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37 597 Title: Figure 4. One-year cumulative outcomes. The cumulative probabilities of (*left*) re-
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39 598 amputation procedures and (*right*) survival are shown for patients that received major (AKA
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41 599 and BKA) and minor lower extremity amputations

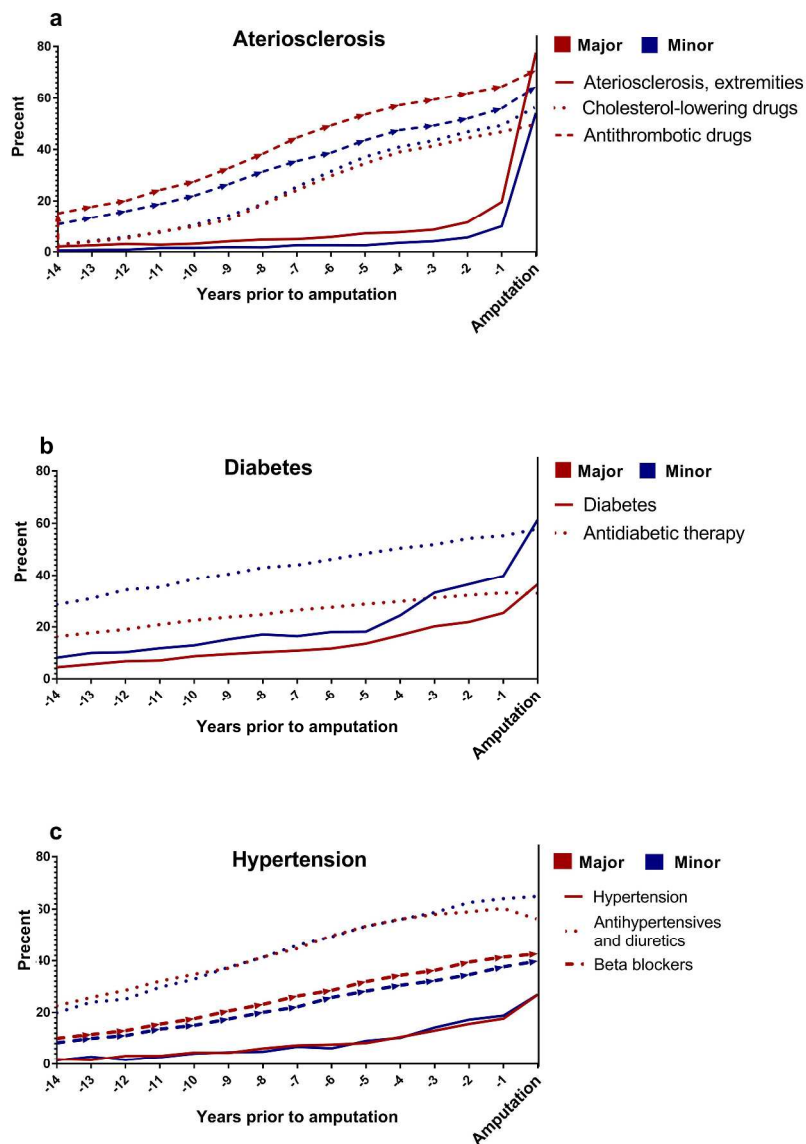
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32 Title: Figure 1. Flowchart shows study selection of patients with lower extremity amputations between
33 01.01.2010 -31.12.2011 in Denmark

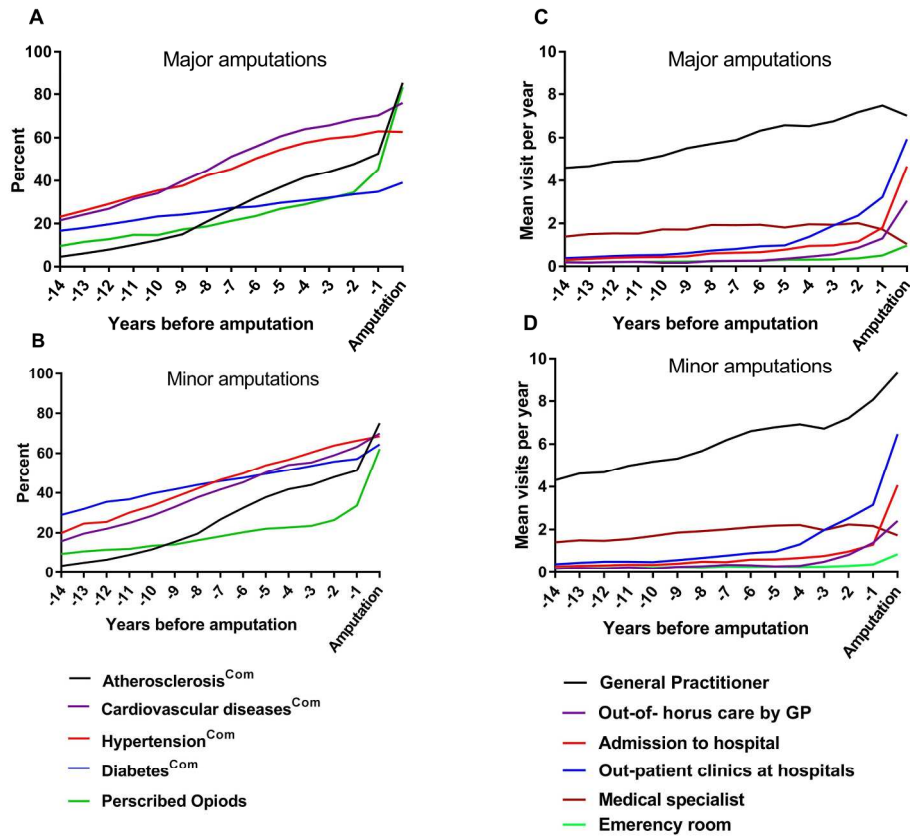
34 Legends: (1) Excluded due to previous amputation define as amputation on the same level or bilateral
35 amputation on a higher level than the index amputation in 2010-11; (2) include hip-exarticulation; (3)
36 include knee disarticulation.

37 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.

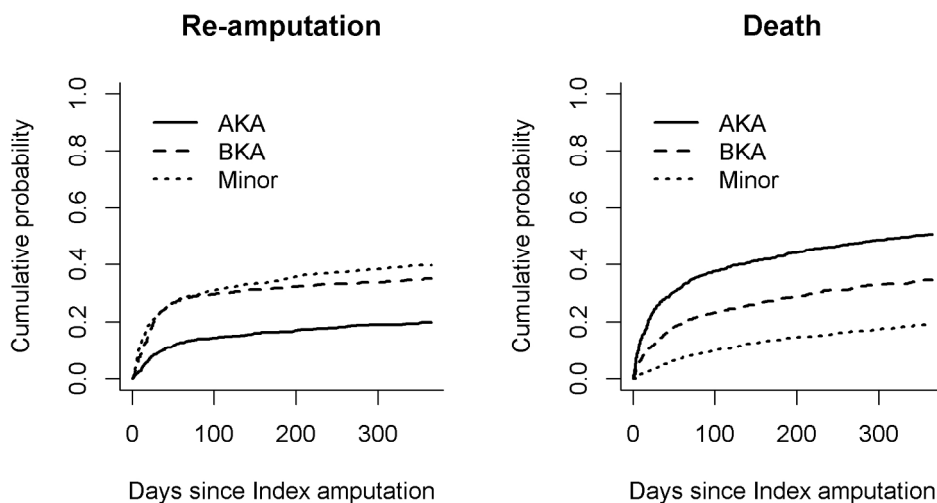
285x396mm (300 x 300 DPI)



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)

Review only

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	DI97, DL88, DI89, 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, DI15
Drugs for hypertension	ACT code C02DB, C02CA, C03AA, C08, C09

Prescribed opioids

ACT code, opioids	ACT code N02A, R05DA04
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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}	
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In risk of LEA

Group "CVD" and "Diabetes ^{Com} " combined	
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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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Page 10, (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	Page 10, (Table1)
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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 13 Tabel 1
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.