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Epidemiology of Major Amputation Following Diabetic Foot Ulcer: Insights from Recent Nationwide Data in the French National Health Registry (SNDS)

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Keywords:

Amputation; Diabetic foot ulcer; Epidemiology; French National Health Data System.

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Abstract

Objective:

The out-of-hospital care pathways of people with DFU have been little studied. We used the French National Health Data System (SNDS) to collect refund and care pathway data for all French residents. The aim of this study was to determine the incidence of major lower limb amputation (MA) and associated risk factors in a population with an incident DFU.

Research design and methods:

We included any person living with diabetes and incident DFU. The primary endpoint was the occurrence of MA within one year. We considered the course and consumption of care one year before and one year after the initial event.

Results:

In 2018, 133,791 people were included, and during the follow-up, MA was performed in 4,733 (3.5%). Among these people with MAs, 16.4% were included via the out-of-hospital part of the protocol, and their first contact with the hospital led to MA. Factors associated (hazard ratio, HR [95% confidence interval, CI]) with MA were: being male (1.92 [1.78;2.08]), arteriopathy of the lower limb (10.16 [9.36;11.03]), psychiatric disease (1.10 [1.01;1.20]) and end-stage renal disease (2.12 [1.93;2.33]). Regarding the care pathway, associations (HR [95%CI]) were observed between lower MA rates and people with more general practitioner (0.83 [0.75-0.91]), private nurse (0.88 [0.81-0.95]) and diabetologist (0.88 [0.81-0.95]) visits. Living in the most disadvantaged municipalities was associated (HR [95%CI]) with a higher MA rate (1.17[1.06-1.29]).

Conclusion:

This is the first national study of the care pathways followed by people with DFU. Failures in the care pathway, precariousness and several comorbidities were identified, with an impact on the MA risk.

Highlights:

- Care pathways of people with diabetic foot ulcer (DFU) and its impact on wound prognosis are poorly studied.
- We found known negative prognostic factors as well as others less well explored, such as psychiatric diseases.
- Inclusion in care pathways and living in less disadvantaged areas are associated with fewer major amputations.
- A large number of amputations are not preceded by a hospitalization for DFU.
- These results emphasize the need for multidisciplinary work through coordinated care pathways to avoid major amputations in people with DFU.

Introduction

Rationale

Diabetic foot ulcer (DFU) is a growing epidemic with extensive social cost [1]. DFU prognosis is uncertain and complications include minor or major amputations, constituting the second social cost of DFU [2]. These complications and the associated mortality rate justify careful studies of the multiple factors associated with wound healing.

Beyond the comorbidities associated with the risk of amputation, a better understanding of the care pathways followed by people with DFU is needed, as are the key factors associated with a better prognosis of these wounds.

Unfortunately, the major studies investigating amputation risk factors only consider crude rates of amputation, without tracking the evolution of the people with DFU [3-5]. The International Working Group on the Diabetic Foot (IWGDF) recommends global care from a multidisciplinary team – with medical, nurse and podiatry consultations and the management of diabetic complications – and follow-up of affected people both in their homes and in the hospital [6]. However, this global approach to care can be complex to set up for people with DFU receiving care outside the hospital. Furthermore, we have few assessments of how these recommendations are implemented in practice.

The National Health Data System (SNDS) collects all French health insurance claim data. This system, considered universal, covers over 99% of the population. In addition to reimbursement data, hospital diagnoses are included through the Information Systems Medicalization Program (PMSI), as is the place of residence of beneficiaries. These residency data can be coupled with data on medical demographics or precariousness in French municipalities [7]. We previously exploited the SNDS at a regional scale, including 15,000 people with incident DFU [8, 9]. We highlighted the link between municipal residency precariousness and major amputation (MA) risk in people with DFU. Territorial accessibility to a nurse was associated with a lower MA rate [8]. Similarly, people with DFU benefiting from more optimal diabetes management – e.g., through annual ophthalmological follow-up – also had lower a risk of MA.

Further, people with DFU and receiving cardiovascular treatment, neurological treatment or antibiotics were at lower MA risk, suggesting that those with more comorbidities had more intensive and efficient treatment. This coupled with the subrisk among those benefiting from an ophthalmological consultation suggested that the markers of a high-performance care pathway were associated with a reduced risk of MA [9].

Based on these data, it seemed important to perform the same analysis with a larger cohort at the national level.

Objectives

The main objective of our study was to analyze the factors associated with MA at one year in people with incident DFU using the French SNDS database at a national scale. Items investigated included supply of care, consumption of care and precariousness of place of residence.

Methods

Settings and study design

We conducted a retrospective study covering the whole territory of France, with French overseas administrative districts included, using SNDS data. The inclusion period began on 1 January 2017 and ended on 31 December 2018. We decided not to take the Covid years into account: thus, to avoid the 2020 data, with a follow-up period of one year, the last inclusion was 31 December 2018. We examined healthcare pathways one year before inclusion and those included were followed for one year after the date of inclusion.

Data source

The SNDS contains several pseudonymized medical-administrative databases.

The French National Hospital Discharge database (PMSI) contains all hospitalization data from private and public hospitals (mainly entry and discharge dates, all medical diagnoses, all medical procedures). Diagnoses are coded according to the International Classification of Diseases, 10th Revision (ICD-10).

The National Health Insurance System (NHIS) database (DCIR) contains sociodemographic data (year of birth, sex), information related to long-term diseases (LTDs), outpatient drug delivery data (dates of delivery, drug name coded according to the Anatomical Therapeutic Chemical classification, amount dispensed), physician and paramedical consultations, and medical acts.

The NHIS assesses the PMSI and DCIR data every year to determine whether French residents are affected by a list of acute or chronic diseases, using validated algorithms [10]. These data are gathered in the Healthcare Expenditures and Conditions Mapping database (HECM).

Participants

We used the same algorithm as the one we used at the regional level [8]. We included people above 18 years old living with diabetes and with an incident DFU. Participants had to be identified as living with diabetes in the HECM [11]. An incident DFU was defined as a DFU occurring during the inclusion period without another DFU in the previous year of the index wound.

A DFU was defined *i*) through the PMSI with a primary diagnosis of DFU [12] (See Table S1; see supplementary materials associated with this article on line), in which case, the date of the beginning wound was the first day of the hospital stay, or *ii*) through an algorithm for out of hospital care refund:

- Two bandage refunds for at least one month, as defined by the IWGDF, and

- The refund of a weekly visit by a private nurse for at least one month from the date of the first bandage refund.

We excluded those who were hospitalized with a diagnosis of decubitus ulcer, a burn of any kind, or after surgery unrelated to the lower limb in the month before the inclusion period (See Tables S2 and S3, see supplementary materials associated with this article on line). We also excluded women with gestational diabetes (defined as the use of antidiabetic drugs during pregnancy but not in the 6 months following pregnancy) and people living in a residential institution for dependent elderly persons (*Etablissement d'Hébergement pour Personnes Agées Dépendantes*: EHPAD) or a long-term care unit. We also excluded twins because of potential individual data-linking problems due to the algorithm for pseudonymization.

We only considered incidental wounds, with the exclusion of people corresponding to the inclusion criteria in 2016.

Variables

The primary outcome was MA (midfoot amputations and above, Table S1; see supplementary materials associated with this article on line) within the year following inclusion. We also examined the variables that can influence DFU prognosis.

Comorbidities

Comorbidities like cardiovascular disease, coronary disease, history of stroke, chronic heart failure, arteriopathy of the lower limb, history of cancer, active cancer (people with a hospitalization or a refund for treatment in direct relation with a cancer in the 2 years before inclusion), psychiatric disease, end-stage renal disease, and liver and exocrine pancreatic disease were considered (HECM database). The updated Charlson score was also calculated [13].

Healthcare pathways

Refunds for certain drugs such as insulin, GLP-1 receptor agonists (GLP-1 RAs), antiplatelet drugs, and lipid-lowering and antihypertensive treatment were included in the analysis, as were refunds for offloading shoes.

We considered all-cause hospitalization the year before inclusion and the number of consultations with a general practitioner (GP), diabetologist, ophthalmologist, nurse or podiatrist.

Healthcare access

We considered the potential localized accessibility (*Accessibilité potentielle localisée*: APL) to GPs and private-practice nurses, a variable built by the French regulatory authorities as the

standardized number of consultations available in a territory [14]. We used the last available index, calculated in 2018.

Deprivation and characteristics of the living municipality

Deprivation at the living-area level was assessed using the revised fDEP 2015, the French deprivation index [15]. Positive fDEP indicates more deprived municipalities.

In France, municipalities are divided as follows: rural: very sparsely populated; rural: sparsely populated; rural: under weak influence of a hub; rural: under strong influence of a hub; and urban: intermediate density or dense.

Statistical methods

Study population characteristics were described with numbers (percentage) for categorical variates and mean \pm standard deviation (SD) for quantitative data. For comparisons between groups, Student's t-test was used when the distribution was Gaussian, and Mann-Whitney otherwise. For qualitative variables, the chi square test was used.

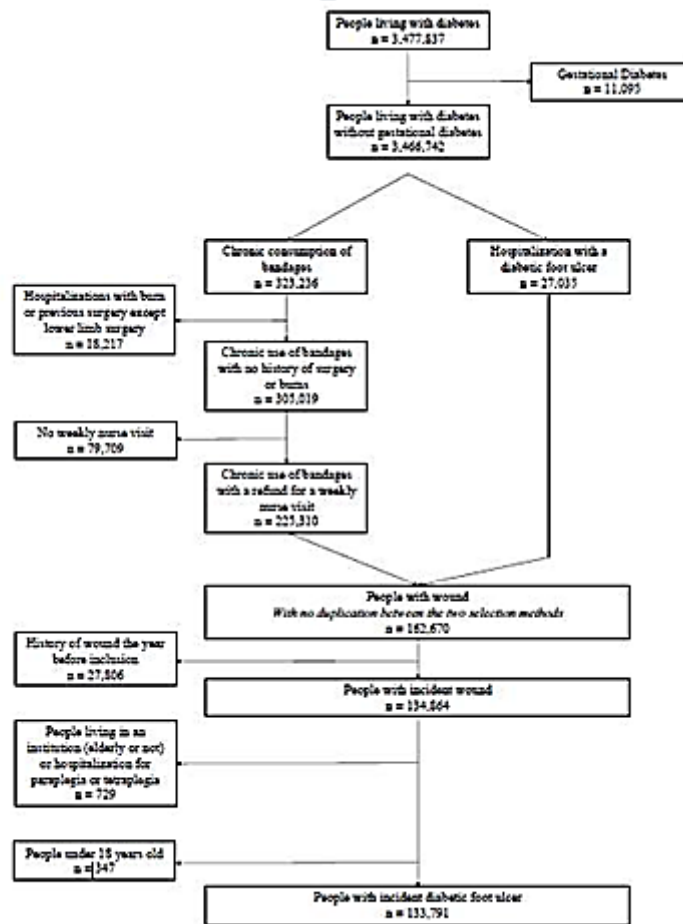
To analyze the factors associated with MA at one year in people with incident DFU, a Cox model was performed for the time without amputation, before and after adjustment. People were censored at the earliest date between death and one-year follow-up. Relevant covariates with a P -value ≤ 0.20 in the univariate analysis were included in the model. We did not include offloading shoes because of a strong indication bias after DFU incidence, and therefore a strong collinearity between these variables. Likewise, we did not include the Charlson index in models already including several conditions as separate variables. Continuous variables which were not log-linear were dichotomized according to their median or deciles (the most discriminant threshold was chosen). The final model was determined using a backward selection based on the Akaike information criterion and the results were then presented with crude and adjusted hazard ratios (cHR and aHR) with 95% confidence intervals (95%CI).

The statistical significance was set as 0.05 and analyses were conducted using Statistical Analysis Systems version 7.13 (SAS Enterprise Guide).

Ethics

The study was reviewed and approved by the Institutional Review Board of the University Hospital of Montpellier, France (identification number: IRB-MTP_2022_05_202201128). It should be noted that research teams from French university hospitals have permanent access to SNDS data [16].

Figure 1: Flow Chart



Results

We identified 3,466,742 people with diabetes mellitus. Among them, 133,791 matched the inclusion criteria, including 27,035 (20.2%) with a hospital diagnosis of DFU and 106,756 (79.8%) from the out-of-hospital algorithm (Figure 1). Among these 106,756 people, 18,672 (14.0%) were subsequently hospitalized with a diagnosis of DFU.

Table I: Description of the population (n=133,791)

Characteristics	
Age, years	72.7 (\pm 13.1)
Male, n (%)	72 243 (54)
Hospitalization for DFU, n (%)	27 035 (20)
Comorbidity	
Cardiovascular disease, n (%)	77 531 (58)
Coronary disease, n (%)	32 406 (24)
History of stroke, n (%)	11 438 (9)
Chronic heart failure, n (%)	17 698 (13)
Arteriopathy of the lower limb, n (%)	30 202 (23)
History of cancer, n (%)	32 229 (24)
Active cancer*, n (%)	20 922 (16)
Psychiatric disease, n (%)	15 498 (12)
Dementia, n (%)	10 442 (8)
End-stage renal disease, n (%)	5 106 (4)
Dialysis, n (%)	4 147 (3)
Liver or exocrine pancreatic disease, n (%)	10 393 (8)
Charlson score, n (%)	3.26 (\pm 4.29)
Charlson score, n (%)	43 088 (32)
1-2	39 826 (30)
3-4	22 020 (16)
≥ 5	28 857 (22)
Current treatment	
GLP-1-RA treatment, n (%)	8 073 (6)
Insulin use, n (%)	49 179 (37)
Antihypertensive treatment, n (%)	112 516 (84)
Platelet antiaggregant treatment, n (%)	62 570 (47)
Lipid-lowering treatment, n (%)	74 465 (56)
Offloading shoes, n (%)	16 101 (12)
Healthcare pathway**	
All-cause hospitalization, n (%)	75 665 (57)
Hospitalization length, days	13 (\pm 35)
General practitioner consultation, n (%)	131 869 (99)
Number of general practitioner consultations, number per month	1 (\pm 1)
Private nurse consultation, n (%)	118 396 (88)
Number of private nurse consultations, number per month	12 (\pm 21)
Ophthalmologist consultation, n (%)	59 581 (45)
Diabetologist consultation, n (%)	22 142 (17)
Podiatrist consultation, n (%)	34 653 (26)
Number of podiatrist consultations, number per month	1 (\pm 2)
Access to care	
Nurse – APL 2018, mean	163.8 (\pm 99.6)
General practitioner – APL 2018, mean	4.1 (\pm 1.2)

Demographic characteristics of the municipality

Municipality type of area, n=125,372	
Rural - sparsely populated, n (%)	16 410 (13)
Rural - very sparsely populated, n (%)	2 769 (2)
Rural - under weak influence of a hub, n (%)	11 214 (9)
Rural - strongly influenced by a hub, n (%)	11 016 (9)
Urban intermediate density, n (%)	38 963 (31)
Dense urban, n (%)	45 000 (36)
Deprivation index Fdep 2015, mean	0.4 (\pm 1.5)

Outcomes

Amputation, n (%)	4 733 (4)
Death, n (%)	19 521 (15)

* Treatment or hospitalization for cancer in the two years before inclusion.

** The year before inclusion.

Data displayed are mean (\pm SD), unless otherwise indicated, or frequency (percentage). APL: *Accessibilité potentiel localisée* (potential localized accessibility).

DFU: Diabetic foot ulcer.

A description of the population is presented in Table I. Fifty-four percent of the population were male. Mean age was 72.7 (\pm 13.1) years. Regarding comorbidities, 58% were identified as having cardiovascular disease, including 24% with a history of coronary disease, 9% with stroke and 23% with arteriopathy of the lower limb. Twelve percent suffered from psychiatric disease, 8% from dementia and 4% from end-stage renal disease. The mean Charlson score was 3.26 (\pm 4.29).

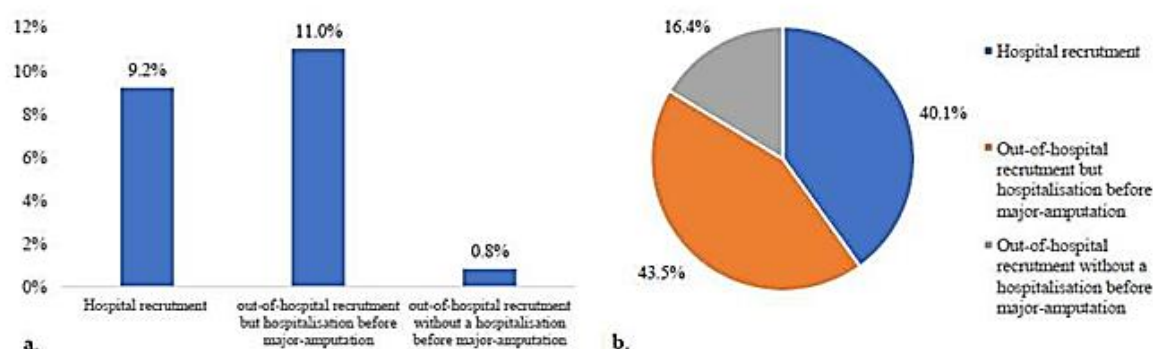
Regarding current treatment, 84% were taking antihypertensive drugs, 47% antiplatelet drugs, and 56% lipid-lowering drugs. Thirty-seven percent had used insulin the year before the wound and 6% had used GLP-1 RAs. Twelve percent of the population was refunded for offloading shoes in the year before the wound.

Nearly all had had a consultation with a GP (99%) and 88% with a private nurse. Seventeen percent had a consultation with a diabetologist the year before the wound and 26% with a podiatrist. Fifty-seven percent had been hospitalized in the year before the wound without an identified diagnosis of DFU.

Regarding the demographic characteristics of the municipalities, information was available for 125,372 people. The mean deprivation index was 0.4 \pm 1.5).

During the year after the DFU diagnosis, 4733 (3.5%) MAs were listed, and 19,521 (14.6%) people died. The MA rate was 9.2% among people recruited through a hospital diagnosis of DFU, 40.1% of all MA. Among the people recruited from the out-of-hospital algorithm, the MA rate was 2.7%. However, 2060 (11.0%) people recruited from the out-of-hospital algorithm but secondarily hospitalized with a diagnosis of DFU (without amputation during this hospitalization) had an MA. They represented 43.5% of all MA. Among those recruited by the outpatient algorithm who had never been hospitalized, 775 (0.83%) had an MA. These people with no hospitalization before MA represented 16.4% of them (Figure 2).

Figure 2: a. Major amputation rate by recruitment method. b. Proportion of major amputations by recruitment method.



The amputations and death occurred respectively on average 3.2 (+/-3.3) and 5.9 (+/- 3.3) months post-diagnosis of DFU. The factors associated with an amputation one year after the DFU are presented in Table II.

Table II: Predictive factors of amputation one year after diabetic foot ulcer diagnosis

	Univariate analysis		Multivariate analysis	
	cHR [95%CI]	P-value	aHR [95%CI]	P-value
Characteristics				
Hospitalization for DFU	6.33 [5.97;6.70]	< 0.0001	2.95 [2.76;3.15]	< 0.0001
Male	2.90 [2.71;3.10]	< 0.0001	1.92 [1.78;2.08]	< 0.0001
Age, per ten years	0.93 [0.91;0.95]	< 0.0001	0.99 [0.99;0.99]	<0.0001
Comorbidity				
Cardiovascular disease	7.57 [6.86;8.35]	< 0.0001	-	
Coronary disease	2.25 [2.12;2.38]	< 0.0001	1.13 [1.05;1.20]	< 0.001
History of stroke	1.72 [1.58;1.87]	< 0.0001	1.10 [1.00;1.20]	0.05
Chronic heart failure	2.08 [1.94;2.23]	< 0.0001	1.32 [1.22;1.42]	< 0.0001
Arteriopathy of the lower limb	16.45 [15.29;17.70]	< 0.0001	10.16 [9.36;11.03]	< 0.0001
Active cancer *	0.48 [0.43;0.54]	< 0.0001	0.75 [0.67;0.84]	< 0.0001
Psychiatric disease	1.23 [1.13;1.34]	< 0.0001	1.10 [1.01;1.20]	0.03
Dementia	1.21 [1.09;1.34]	< 0.001	-	
End-stage renal disease	4.76 [4.39;5.16]	< 0.0001	2.12 [1.93;2.33]	< 0.0001
Liver or exocrine pancreatic disease	1.22 [1.11;1.35]	< 0.0001	0.84 [0.76;0.93]	< 0.01
Charlson score, per point ^a	1.02 [1.01;1.02]	< 0.0001		

Current treatment				
Insulin use	1.83 [1.77;1.99]	< 0.0001	1.28 [1.20;1.37]	< 0.0001
GLP-1-RA treatment	0.82 [0.72;0.94]	< 0.01	-	
Antihypertensive treatment ^a	1.00 [0.92;1.08]	0.93	-	
Platelet antiaggregant treatment	1.83 [1.73;1.94]	< 0.0001	-	
Lipid-lowering treatment	1.09 [1.03;1.16]	< 0.01	0.81 [0.76;0.87]	< 0.0001
Offloading shoes ^a	1.65 [1.53;1.77]	< 0.0001	-	
Healthcare pathway ^{**}				
All-cause hospitalization	1.23 [1.16;1.30]	< 0.0001	0.91 [0.85;0.97]	< 0.01
Number of general practitioner consultations (<i>per month</i>), > 0.33 vs. ≤ 0.33 [§]	0.49 [0.45;0.53]	< 0.0001	0.86 [0.79;0.95]	< 0.01
Private nurse consultation	0.68 [0.63;0.74]	< 0.0001	0.87 [0.80;0.95]	< 0.01
Ophthalmologist consultation	0.87 [0.82;0.92]	< 0.0001	-	
Diabetologist consultation	1.18 [1.10;1.27]	< 0.0001	0.89 [0.82;0.96]	< 0.01
Podiatrist consultation	1.30 [1.22;1.38]	< 0.0001	1.08 [1.01;1.16]	0.02
Access to care				
Nurse – APL 2018, > 138.6 vs. ≤ 138.6 [§]	0.89 [0.84;0.94]	< 0.0001	0.89 [0.84;0.95]	< 0.001
General practitioner – APL 2018, > 2.55 vs. ≤ 2.55 [§]	0.89 [0.81;0.98]	< 0.01	-	
Demographic characteristics of the municipality				
Municipality type of area ^a				
Rural, sparsely populated				
Rural, very sparsely populated	0.92 [0.74;1.14]	0.44	-	
Rural, under weak influence of a hub	0.96 [0.85;1.10]	0.57	-	
Rural, under strong influence of a hub	0.93 [0.82;1.06]	0.29	-	
Dense urban	0.99 [0.91;1.08]	0.85	-	
Deprivation index Fdep 2015, ≥ 2.33 vs. < 2.33 [§]	1.08 [0.98;1.19]	0.14	1.17 [1.06;1.29]	< 0.01

* Treatment or hospitalization for cancer in the two years before inclusion.

** The year before inclusion.

§ 0.33 is the first decile; 138.6 is the median; 2.55 is the first decile; 2.33 is the 9th decile.

^a Variables were not candidate in multivariate analysis

cHR: crude hazard ratio, aHR: adjusted hazard ratio, CI: confidence interval

Males, younger people, and those hospitalized for the DFU had poorer MA rates. The comorbidities especially associated (HR[95%CI]) with a higher MA rate were arteriopathy of the lower limb (10.16[9.36;11.03]), end-stage renal disease (2.12[1.93;2.33]), chronic heart failure (1.32[1.22;1.42]) and psychiatric disease (1.10[1.01;1.20]). An active cancer (0.75[0.67;0.84]) and liver or exocrine pancreatic disease (0.84[0.76;0.93]) were associated with a lower rate of MA.

Insulin use was associated (HR[95%CI]) with a higher risk of MA (1.28[1.20;1.37]) as opposed to lipid-lowering medication use (0.81[0.76;0.87]). Subjects hospitalized for all causes (0.91[0.85;0.97]), with more than 0.33 GP visits per month (0.86[0.79;0.95]), private

nurse visits (0.87[0.80;0.95]) or diabetologist consultations (0.89[0.82;0.96]) had lower MA rates.

Better access to a private nurse was associated (HR[95%CI]) with a lower MA rate (0.89[0.84;0.95]). Access to a GP was no longer associated in the multivariate analysis. Living in the most disadvantaged decile of municipalities was associated with a higher MA rate (1.17[1.06;1.29]).

Discussion

To our knowledge, this study offers the largest survey of DFU to date. We identified nearly 134,000 people with incident DFU by consulting the universal health claim database of the French social security system, the SNDS. Of these people, 3.5% had had a major amputation in the year after diagnosis.

We identified several factors associated with lower limb amputation. Certain well-known comorbidities were linked to higher amputations rates, such as arteriopathy of the lower limb [17], coronary disease [18] and end-stage renal disease [19], a condition which shares the same overall characteristic of distal arterial involvement as diabetes [20, 21]. Notably, we highlighted the link between psychiatric disease and amputation, finding that this population is at risk and often in difficulty in the care pathways [22, 23]. This association has been described for depression [24] but research is still lacking for pathologies such as schizophrenia. Research by type and severity of psychiatric pathology would be relevant in view of their independent effect on the risk of MA.

Inclusion in a care pathway that took into account consultations with various professionals was linked to a reduction in the MA rate. Similarly, better access to primary care, in this case private nursing consultations, was also linked to a lower one-year MA rate. Not least, people living in the most socially deprived communes had a higher MA rate. Previous studies that used the SNDS data have shown around 9000 amputations per year [5]).

We did not obtain this volume, but it should be noted that we only considered MAs, and thus excluded toe amputations, which represent more than 50% of all amputations [12]. We also only considered MAs in the year following an identified incident DFU. Therefore, we excluded most chronic wounds – with treatment over several years – and traumatic wounds – after a car accident, for instance.

We highlighted three subpopulations, which themselves accounted for 40% (first diagnosis of DFU during a hospitalization), 44% (out hospital diagnosis followed by hospitalization for DFU) and 16% (out hospital diagnosis but no hospitalization before MA) of the people who have had an MA. These three populations raise different questions. Why did 20% of people suffering from DFU and 40% of those suffering secondarily from a MA enter the hospital directly, without first undergoing outpatient assessment? What degree of wound severity and what degree of involvement in a care pathway determines rapid hospitalization? Although this study was not designed to address these questions, they seem highly relevant, and each merits further exploration.

Another important point is that we found an association between a decrease in MA rates and advancing age. In our opinion, this should be handled with caution. An analysis of mortality at one year in this cohort would have been relevant before any conclusion could be drawn on this point that is, actually, inconsistent with the literature [25, 26]. However, our cohort was substantially older than those in other reports. We were unable to ascertain whether some people had died before they were able to undergo amputation, or whether the wounds were less severe in these people, or if they were in palliative care. It should be noted that we excluded institutionalized people, and this meant that elderly people in long-term care institutions – and therefore among those receiving the best medical follow-up – were excluded. GLP-1 RAs only appeared in the univariate analysis. It is possible that their effect was masked by other factors and that a longer period of impregnation would be required before results could be obtained for this population. In view of the results concerning protection against cardiovascular risk [27], specific monitoring might well be appropriate for people with or at risk of DFU.

Several elements of care consumption can be highlighted. Only one in two people with DFU received reimbursement for lipid-lowering drugs. The same result was found for antiplatelet drugs despite this cohort being a very high-risk cardiovascular population, with 24% having a documented history of cardiovascular disease and living with an acute DFU. The impact of statins [28] on the prognosis of peripheral artery disease is well-established and these drugs are now recommended for DFU [29]. The impact of antiplatelet drugs, however, is more controversial [30]. The refund rate for an offloading shoe before a DFU diagnosis is difficult to interpret. In a future study, the rate of people who purchase an offloading shoe after the start of DFU should be examined, as should the impact of this purchase on the rate of major amputations.

In line with our regional study, we highlight that accessibility to primary care, especially private nurses, was associated with a reduced rate of MA. Contrary to other studies, access to care seemed to have a greater impact on wound prognosis than did living in a rural area [31]. In general, primary care consultations were linked to a lower amputation rate. The case of consultation with a diabetologist is particularly enlightening. This type of consultation was linked to a higher rate of MA in the univariate analysis but to a lower rate in the multivariate analysis. One assumption is that those with the most complex situations are more likely to consult a diabetologist and therefore will have a worse prognosis. This finding was corrected by the multivariate analysis, which revealed a more reassuring association. These last findings are in favor of the care pathway proposals of the IWGDF [6].

Last, the link between social deprivation and MA corroborates all the previous observations [3, 4, 32, 33]. Unlike other methods of measuring precariousness, the fDEP, which is comparable to the English Index of Multiple Deprivation (IMD) score [34] or the Scottish SIMD [35] score, is a complete score that takes into account a sum of factors, and thus it is not limited to financial insecurity. This social deprivation appears to be independent on comorbidities and access to care. It should be noted that the French social security system is considered universal (including for non-legal immigrant populations). Precariousness therefore affects people with DFU regardless of their access to social security coverage [36]. This should be a major factor in the design of our healthcare system. Unfortunately, we do not have access to individual data on precariousness in the SNDS. Other studies that consider universal health coverage (CMU-C) are constrained to focus on the population under 70, as the French social protection system does not allow for SNDS identification beyond this age group. We decided to take into account the entire population.

The results on psychiatric disease corroborate the issues around access to care and social deprivation. For these most vulnerable populations, the common care pathway does not seem to be enough and/or adapted.

The main limitation of our study is related to our algorithm for DFU in an outpatient setting. We could not be certain that all those included in our study truly had a DFU. However, we carefully excluded situations with a high risk of pressure ulcers, surgical wounds or burns and prevalence is consistent with the literature. Even though we may have concerns about our out-of-hospital algorithm, this recruitment method nevertheless identified 40% of the MA in our cohort for whom doubts about the presence of DFU had not arisen.

We note that the rate of MA and the ratio between in-hospital and out-of-hospital recruitment were all consistent with the results of our previous regional study using the same algorithm (8).

The SNDS only covers reimbursements for drugs and consultations. We therefore did not conduct a study of actual treatment consumption. However, for the bandage protocol, we verified purchase renewals and considered this a probable indicator of consumption. In addition, the exhaustiveness of the data in this universal social security system may help to compensate for this bias.

The SNDS database does not contain data about disease severity, including for diabetes and DFU. It is therefore impossible to know whether a person without insulin has a well-controlled disease or poor medical follow-up, or whether a person who died before amputation was healed from DFU or was, on the contrary, too severely ill to be referred for amputation. In addition, the SNDS database does not differentiate between people living with type 1 or type 2 diabetes.

It is possible that the youngest people using insulin are people living with type 1 diabetes, and that it is this element that has the greatest impact on their risk of MA. Similarly, identifying tobacco users is not feasible, and any attempt to stratify wound severity remains speculative and uncertain.

During the study recruitment period, sodium-glucose cotransporter type 2 inhibitors (iSGLT2is) were not available in France. Their impact, particularly on the amputation rate, could therefore not be studied here.

Our recruitment method inside and outside the hospital opens up the possibility of creating cohorts to monitor DFUs, whereas hospital cohorts by definition only consider people admitted to the hospital and epidemiological studies focus on crude amputation rates without first following people with DFU. Our study therefore has the original advantage of highlighting the factors associated with MA over a wider panel and is thus probably closer to real life. Transposition might be easier for professionals practicing outside the hospital and receiving people with DFU.

The use of a universal database such as the SNDS strengthens the external validity of our study.

The results, however, can only be generalized to countries with similar resources.

Conclusion

In this work we highlight a MA rate of 3.5% in this large cohort of people with DFU. We found that comorbidities, difficulty accessing care, and social deprivation were factors associated with a higher rate of MA. Effective monitoring outside the hospital was associated with better prognosis. At least, 16% of the MAs were carried out in people who had not been treated by a specialized hospital team prior to amputation. These results emphasize the need for multidisciplinary work through coordinated care pathways to avoid major amputations in people with DFU.

Data availability

According to the SNDS rules, data are not available on request from the authors.

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Conflict of Interest

The authors declare that they have no competing interests.

Compliance with ethics guidelines

All procedures performed in studies involving human participants are in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was part of the usual public health assessment of the Regional Medical Department of the *Caisse Nationale d'Assurance Maladie* (CNAM), the national health insurance institution in charge of the SNDS.

Contribution statement

Study concept and design: JBB, AS and CD; Acquisition of data: HH, CD and JBB; Statistical analysis: HH, CD, ST and JBB; Study supervision: AA and AS; Writing the manuscript: JBB, AS and CD. All authors read and approved the final version of the manuscript. Ariane Sultan accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish

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