Five-year mortality in patients with diabetic foot ulcer during 2009–2010 was lower than expected

Coralie Amadou, Aurélie Carlier, Chloé Amouyal, Olivier Bourron, Carole-Elodie Aubert, Thibault Couture, Eric Fourniols, Georges Ha Van, Stéphanie Rouanet, Agnes Hartemann

Five-year mortality in people with diabetic foot ulcer in the years **2009-2010** is lower than expected.

Coralie Amadou*[1], Aurélie Carlier*[1,2,3], Chloe Amouyal[4], Olivier Bourron[1,2,3], Carole Aubert[5], Thibault Couture[3,6], Eric Fourniols[7], Georges Ha Van[1], Stéphanie Rouanet[8], Agnes Hartemann [1,2,3]

[1]Diabetology department, AP-HP, Pitié-Salpêtrière Hospital, 83 bld de l'hôpital, F-75013 Paris, France
coralie.amadou@gmail.com;olivier.bourron@aphp.fr;georges.havan@aphp.fr; agnes.hartemann@aphp.fr
[2]Inserm, CIC-1421, AP-HP, Pitié-Salpêtrière Hospital, Department of Pharmacology, 83 bld de l'hôpital F-75013 Paris, France
aurelie.carlier@aphp.fr
[3]Sorbonne Université, 91 bld de l'hôpital F-75013 Paris, France
[4]Sorbonne-Université, Inserm, Research Unit on Cardiovascular, Metabolic And Nutrition Diseases (UMRS-1166), Institute of Cardiometabolism and Nutrition, 91 bld de l'hôpital F-75013 Paris, France
chloe.amouyal@gmail.com
[5]Department of internal medicine, Fribourg Hospital, Switzerland
CaroleElodie.Aubert@insel.ch
[6]Department of vascular Surgery, AP-HP, Pitié-Salpêtrière Hospital, 83 bld de l'hôpital F-75013 Paris, France
thibault.couture@aphp.fr
[7]Department of orthopedic Surgery, AP-HP, Pitié-Salpêtrière Hospital, 83 bld de l'hôpital F-75013 Paris, France
eric.fourniols@aphp.fr
[8]StatEthic SASU73 rue Paul Vaillant Couturier,92300 Levallois-Perret,France
stephanie.rouanet@statethic.fr

* These authors contributed equally to the work

Corresponding author:

Agnès Hartemann: Diabetes department, Pitié-Salpetrière Hospital, 83 bld de l'Hôpital, 75013 Paris France

e-mail agnes.hartemann@aphp.fr

Word count: 2280

Tables: 2; Figures: 2

Abstract

Aim

Mortality rate is decreasing in people with diabetes but if this observation also concerns patients with diabetic foot ulcer (DFU) needs additional data. This study evaluated the mortality rate at 5 years in patients with a DFU occurring in the years **2009-2010** and **identified risk factors associated with mortality.**

Methods

Patients who successively attended for a new foot ulcer between in 2009-2010 were followed until healing and at one year. Data on mortality were collected at year 5. **Multivariate Cox proportional Hazard model** was used to identify mortality risk factors.

Results

Three hundred and forty-seven patients were included: mean age was 65±12 y, diabetes duration was 16 [10; 27] years; 13 % were on dialysis and 7 % had an organ graft. At 5 years, 49 patients (14%) were considered lost to follow up. The total mortality rate at 5 years was 35 %, and 16% in patients with neuropathy. In multivariate analysis, mortality was positively associated with age (HR 1.05 [1.03-1.07], p < 0.0001); duration of diabetes (HR 1.02 [1.001-1.03], p = 0.03); PEDIS perfusion grade 2 vs 1 (HR 2.35 [1.28-4.29], p = 0,006); PEDIS perfusion grade 3 vs 1 (HR: 3.14 [1.58-6.24], p=0.001), and **with the duration of ulcer during the first year** (HR 2.09 [1.35-3.22], p=0.0009).

Conclusion

Mortality rate was not as high as expected despite a high number of co-morbidities, suggesting that progress has been made in health care of these patients. Particularly, patients with neuropathic foot ulcer had a survival rate at 5 years of 84%.

Key words

Diabetes. Foot. Ulcer. Mortality.

Abbreviations

ABI Ankle brachial index

CLI Critical limb ischemia

DFU Diabetic foot ulcer

PAOD Peripheral artery occlusive disease

PEDIS Perfusion, Extent, Depth, Infection, Sensation

Introduction

Diabetic foot ulcer (DFU) is an economic burden for many countries and induces a dramatic decrease in physical, emotional, and social functioning for patients [1, 2]. It is associated with advanced micro and cardiovascular complications, resulting in high morbidity and a greater risk of premature death [3]. The major cause of death in DFU is ischemic heart disease [4, 5].

Studies regarding long term survival in patients with DFU are scare, but data coming from cohorts formed before the 2000s, reported mortality rates around 45% at five years [4-6]. However life expectancy has improved for the last years in people with diabetes [7, 8], and therapeutic options for DFU have made progresses and are now the topic of robust international guidelines [9]. A single study in 2008 [5] suggested that survival in people with DFU before and after the 2000s could have increased, but these optimistic results were not confirmed in another study published in 2012 [10].

The main aim of our study was thus to determine the years 2010 life expectancy in patients with DFU. Identifying patients with DFU who are at high risk of premature death is important to choose the best therapeutic project with each patient. Thus secondary objective was to identify the years 2010 predictive factors for five-year mortality in patients with DFU.

Methods

Population

Between March 2009 and December 2010, all patients with diabetes and a new foot ulcer who attended a multidisciplinary diabetic foot center in a University Hospital (Paris, France), were successively included in this cohort. Patients gave oral consent for participation and agreed to be contacted (them or their family relatives) to obtain information on their outcomes. The study was in accordance with ethical legislation in France.

ClinicalTrials.gov registration no. NCT03782129

Wound healing date was recorded until 12 months after inclusion. Five years after inclusion, patients or their family relatives or their family physician were contacted by phone

to know if they were still alive. If necessary we consulted clinical files or the registry office of the patient's birth town hall. If there was no mention of death on birth certificate, the patient was considered to be still alive. If the patient was not born in France, and the information could not be obtained, the patient was considered lost to follow-up.

Foot ulcer management

All patients with DFU were treated according to the most recent guidelines from the International Working Group on the Diabetic Foot (IWGDF), particularly for Peripheral Artery Occlusive disease (PAOD), and the French Society of Infectious Diseases. Hospitalization was required in case of wound complications.

Database

At inclusion data were collected for the following variables: age, sex, diabetes type and diabetes duration, insulin therapy, BMI, dialysis, kidney or pancreas-kidney transplant, active smoking, presence of a relative at home or not, date of ulcer occurrence, history of previous DFU or amputation. Severity of ulcer was graded according to the University of Texas Diabetic Wound Classification System [11] and to the PEDIS (Perfusion, Extent, Depth, Infection, Sensation) classification system [12].

In the PEDIS classification **peripheral arterial occlusive disease (PAOD)** is grade 2 if presence of symptoms or signs of PAOD but not of critical limb ischemia (CLI): presence of intermittent claudication or Ankle Brachial Index (ABI) <0.9 (but with systolic ankle pressure >50 mmHg) or Toe brachial Index <0.6 (but with systolic toe blood pressure >30 mmHg) or **Transcutaneous Pression of O2** (TcPO2) is 30-60mmHg or other abnormalities on non-invasive testing, compatible with **peripheral arterial disease** but not with **critical limb ischemia**. **Peripheral arterial disease is** grade 3 (**critical limb ischemia**) if systolic ankle blood pressure is < 50 mmHg or systolic toe blood pressure is < 30 mmHg or TcPo2 < 30 mmHg.

The PEDIS classification for sensation is as follow: grade 1= a normal sensation, grade 2 = a loss of sensitivity to the monofilament, and grade 3= presence of a chronic Charcot foot.

Objective and outcome

The objective of our study was to determine mortality rate at 5 years. The secondary objective was to identify the independent predictors of five-year mortality in patients with **diabetic foot ulcer.**

Statistical analysis

Continuous variables are reported as mean ± standard deviation (sd) or median [Q1; Q3] and are compared using Wilcoxon rank sum test. Categorical variables are reported as number and percentage (percentages were calculated excluding missing data) and are compared by Chi-2 lcertest or Fisher's exact test, as appropriate. Missing data had not been **imputed**.

Time to death after inclusion was analyzed using Kaplan Meier method. Estimate rate at 1, 3 and 5 years and their 95% confidence interval (CI) are presented. Patients who were known to be alive at five-year or lost-to follow up were censored **at five years or at the last contact date**. For some patients, information on death was known, but the date of death could not be recovered. In order to take these patients into consideration, 2 analyses were performed: these patients were considered as deceased at the latest available date of follow-up plus 1 day (primary analysis) and censored at the latest available date of follow-up (sensitivity analysis).

Risk factors of death were looked for among patients' and disease' characteristics (age, sex, ulcer duration, body mass index (BMI), lifestyle, type 2 diabetes, insulin treatment, diabetes duration, hemodialysis, active smoking, PEDIS perfusion, PEDIS sensation, University of Texas Diabetic Wound Classification System, acute hospitalization and **ulcerduration during the first year of follow up** (as time-dependent covariate) using Cox proportional Hazard model. **Univariate analysis (p<0.15) were first performed to select potential explanatory variables that were subsequently tested in multivariate model (stepwise method).** The results **were** interpreted in terms of adjusted hazard ratios (aHR) with their associated 95% CI.

A p-value <0.05 was considered significant. All statistical analyses involved the use of SAS release 9.4 (SAS Institute Inc, Cary, NC) statistical software package.

Results

Three hundred and forty-seven (347) patients were included. Five years after inclusion 49 (14%) patients were lost to follow up (Figure 1).

The main characteristics of the patients at inclusion are given in Table 1. **Sixty eight** % were male and mean age was 65 +/- 12 years. Most patients were retired (62 %) and **did not live alone** (77 %). **Eighty nine** % had type 2 diabetes, 71 % were treated with insulin and duration of diabetes was 16 [10; 27] years. **Fourteen** % of patients were active smokers, 13% were on dialysis and 7 % had a organ transplant (4% a kidney and 3% a kidney-pancreas transplant). **Seventy** % of patients had **peripheral arterial disease (PAOD)** and 17 % had grade 3 PAOD according to PEDIS classification (e.g. supplemental Table S1). **Nine** % of patients had grade

3 neuropathy (**chronic Charcot foot**) according to PEDIS sensation classification. 50% of patients **were admitted to hospital at baseline** for wound management.

Median wound duration at inclusion was 49 [19; 120] days. The distribution of ulcer gradation according to PEDIS classification and University of Texas Diabetic Wound Classification System is given in supplemental Tables S1 and S2.

Compared with **patients not lost to follow-up (N=298)**, patients lost to follow up **(N=49)** had a longer ulcer duration at inclusion (66 [30; 155] versus 46 [18; 114] days; p=0.04), a more frequent grade 4 infection (6% versus 0.3%; p=0.018) and they required more frequently to be admitted (68 versus 48%; p =0.02). But they were not different for age, diabetes duration, severe comorbidity like dialysis or organ graft, and pedis perfusion classification.

According to Kaplan Meier method, the non-healing rate at one year of follow up was 32.8% [27.4; 38.3].

Mortality rate

The five-year mortality rate was 35% [30; 41] **(primary analysis)**. Mortality rate was 10% at year 1 and 25% at year 3. (**Figure 2a**).

Independent predictors of five-year mortality

Mortality at year 5 was associated with age, diabetes duration, dialysis, PEDIS perfusion grade, PEDIS sensation grade, wound University of Texas classification stages **C,D** and **ulcer duration during the first year of follow up** (Table 2).

Independent predictors of five-years mortality were higher age, higher diabetes duration, PEDIS perfusion grade 2 or 3, **and ulcer duration during the first year of follow up** (Table 3). These results were consistent in the sensitivity analyze (data not shown).

Mortality rate according to PEDIS perfusion grade is shown in supplemental table S3 and survival curves in Figure 2b. Patients with grade 1 PEDIS perfusion (no **peripheral arterial disease**, neuropathic foot ulcer) had a survival rate of 100, 91 and 84% at respectively 1, 3 and 5 years.

Discussion

The 5-year mortality rate of patients presenting a new diabetic foot ulcer in the years **2009-2010** was 35%. The most appropriate study to make a comparison with our data is the one of Morbach and col [10] on patients presenting with DFU in 1998-1999, because patients

seems to be nearly comparable. Despite a bit higher rate of severe comorbidities in our cohort compared with Morbach's one (respectively 13% of patients on dialysis versus 4%, 70% of patients with **peripheral arterial disease** versus 55%) we found a lower mortality rate: 35% compared with 46%. Importantly in patients without **peripheral arterial disease** (isolated neuropathy) the mortality rate in our cohort is much smaller (16%) and twice as lower than in the Morbach's cohort (30%). The difference is smaller for patients with **peripheral arterial disease**, but presents: 43% compared with 59%. The mortality rate in our cohort is also lower than in others cohorts followed before the years 2010 [6, 13]. These results suggest that life expectancy has improved in patients with **diabetic foot ulcer**.

Young and col in 2008 [5] already suggested this increase in life survival in patients with **diabetic foot ulcer**. They even reported a low 27% mortality rate, but patients in their cohort were younger than in our (62 years old versus 65) with a shorter duration of diabetes (14 years) and a less frequent **peripheral arterial disease** (50%), all these factors influencing mortality.

Interestingly in a recent national observational study including patients with an active **diabetic foot ulcer** in the 2008-2011 years, identified from a diabetes register, the percentage of people who died during a 2 year follow up period was 16% [14], so next to the one observed in our study (see fig 2).

An improvement in life expectancy has been recently described in people with diabetes (type 1 and type 2) [8]. This is probably explained by a combination of advances [15] among which a better management of cardiovascular risk factors. The first cause of mortality in patients with **diabetic foot ulcer** is a cardiovascular event which explains 50% to 75% of deaths [4, 5, 16], and we can suppose that the better management of cardiovascular risk factors also regard these patients. Another explanation could be the improvement of foot ulcer management observed in the last years, with a lower rate of major amputation when patients are referred to **diabetic foot ulcer** centers, like in the current cohort where the major amputation rate was 10% at year 1 (data not shown). This may improve health related quality of life and decrease depression, two components that are predictive of mortality [17, 18] in this population.

In our cohort, the strongest independent predictive factor of mortality at year 5 was severe **peripheral arterial disease** (grade 3 of the PEDIS classification), which is an expected risk factor for mortality [5, 10]. It is assumed that the severity of **peripheral arterial disease** is a strong reflection of the general health and cardio-vascular patient's condition. Interestingly the **wound duration during the first year** was another important independent factor associated with 5-year mortality (HR: 2.09). To our knowledge, no previous studies have already tested the association with this variable. The persistence of a non-healed foot ulcer exposes to infection, but this is not a frequent cause of mortality, **and PEDIS infection was not associated with mortality in our study (data not shown).** It is more likely that a prolonged non healed ulcer reflects the presence of several factors that may increase the risk

of death, like undernutrition, depression, carelessness and poor adherence to treatments. In the Eurodial study [19] a low health-related quality of life (HRQoL) especially in the physical domain, was associated with death in people with DFU after adjustment for possible confounders. Authors suggested that strategies that improve mobility, reduce pain, and enable patient to better perform daily activities might have beneficial effects on the outcome, in addition to biomedical interventions focused on wound treatment. Depression which can reduce self-care is also associated with mortality at five years in people with **diabetic foot ulcer** [18].

The strengths of our study are the high number of patients, the prospective design and the low rate of lost to follow up. Weaknesses of our study are the monocentric recruitment, the absence of a comparative group, and the absence of data on drug therapies and causes of death.

Conclusions

In the years **2009-2010**, mortality rate at year 5 of patients presenting with a new **diabetic foot ulcer** is not as high as observed before the 2000s, suggesting that these patients benefit of a better health care like all people with diabetes. This result emphasizes that **diabetic foot ulcer** should not be considered as a terminal illness, and that clinicians need to address risk factors for mortality aggressively in these patients to improve chances of survival. Particularly in patients with neuropathic foot ulcer, the chance to be still alive after five years is high: it concerns 84% of patients. Importantly, patients with **a long duration non-healed ulcer** are at high risk of mortality at five year independently of **peripheral arterial disease** and age. These patients could probably have benefit of a better global care, taking into account nutrition, psychological health and daily well-being, but this remains to be tested in future studies.

Acknowledgments

We thank Eli Lilly Company for having supported this work.

Funding

This work was supported by Eli Lilly Company.

Contribution statement

C.A. researched data and wrote the manuscript. A.C. researched data and wrote the manuscript. C.A. contributed to the discussion. O.B. reviewed the manuscript. C.A. researched data. T.C. researched data. E.F. researched data. G.H.V. helped design the study and researched data. SR carried out all statistical analysis and reviewed the manuscript. A.H. designed the study, wrote the manuscript and contributed to the discussion.

A.H. is the guarantor of this work and, has full access to all the data, and takes responsibility for the integrity of the data.

References

[1] Reiber GE, Lipsky BA, Gibbons GW. The burden of diabetic foot ulcers. Am J Surg 1998; 176 (2A Suppl):5S-10S. https://doi.org/10.1016/S0002-9610(98)00181-0

[2] Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005; 366: 1719-24. https://doi.org/10.1016/S0140-6736(05)67698-2

[3] Boyko EJ, Ahroni JH, Smith DG, Davignon D. Increased mortality associated with diabetic foot ulcer. Diabet Med 1996; 13:967-72.https://doi.org/10.1002/(SICI)10969136(199611)13:11<967::AID-DIA266>3.0.CO;2-K

[4] Iversen MM, Tell GS, Riise T, et al. History of Foot Ulcer Increases Mortality Among Individuals With Diabetes. Diabetes Care 2009; 32 :2193-2199. https://doi.org/10.2337/dc09-0651

[5] Young MJ, McCardle JE, Randall LE, Barclay JI. Improved survival of diabetic foot ulcer patients 1995-2008: possible impact of aggressive cardiovascular risk management. Diabetes Care 2008; 31:2143-2147. https://doi.org/10.2337/dc08-1242

[6] Moulik PK, Mtonga R, Gill GV. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. Diabetes Care 2003; 26:491-494. https://doi.org/10.2337/diacare.26.2.491

[7] Dale AC, Vatten LJ, Nilsen TI, Midthjell K, Wiseth R. Secular decline in mortality from coronary heart disease in adults with diabetes mellitus: cohort study. BMJ 2008; 337:99-102. https://doi.org/10.1136/bmj.39582.447998.BE

[8] Rawshani A, Rawshani A, Franzén S et al. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. N Engl J Med 2017; 376:1407-1418. https://doi.org/10.1056/NEJMoa1608664

[9] Bus SA, Armstrong DG, van Deursen RW et al. IWGDF guidance on footwear and offloading interventions to prevent and heal foot ulcers in patients with diabetes. Diabetes Metab Res Rev 2016; 32 Suppl 1:25-36. https://doi.org/10.1002/dmrr.2697

[10] Morbach S, Furchert H, Gröblinghoff U et al. Long-term prognosis of diabetic foot patients and their limbs: amputation and death over the course of a decade. Diabetes Care 2012; 35:2021-2027. https://doi.org/10.2337/dc12-0200

[11] Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care 1998; 21(5): 855-859. https://doi.org/10.2337/diacare.21.5.855

[12] Chuan F, Tang K, Jiang P, Zhou B, He X. Reliability and validity of the perfusion, extent, depth, infection and sensation (PEDIS) classification system and score in patients with diabetic foot ulcer. PloS One 2015; 10:e0124739. https://doi.org/10.1371/journal.pone.0124739

[13] Ghanassia E, Villon L, Thuan dit Dieudonné J-F, Boegner C, Avignon A, Sultan A. Long-Term Outcome and Disability of Diabetic Patients Hospitalized for Diabetic Foot Ulcers. Diabetes Care 2008; 31:1288-1292. https://doi.org/10.2337/dc07-2145

[14] Vadiveloo, T., Jeffcoate, W., Donnan, P.T. et al. Amputation-free survival in 17,353 people at high risk for foot ulceration in diabetes: a national observational study. Diabetologia 2018; 61: 2590-2597. https://doi.org/10.1007/s00125-018-4723-y

[15] Tricco AC, Ivers NM, Grimshaw JM et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. Lancet 2012; 379:2252-2261. https://doi.org/10.1016/S0140-6736(12)60480-2

[16] Chammas NK, Hill RLR, Edmonds ME. Increased Mortality in Diabetic Foot Ulcer Patients: the Significance of Ulcer Type. J Diabetes Res 2010; 2016:2879809. http://dx.doi.org/10.1155/2016/2879809

[17] Williams LH, Rutter CM, Katon WJ et al. Depression and incident diabetic foot ulcers: a prospective cohort study. Am J Med 2010; 123:748-754. https://doi.org/10.1016/j.amjmed.2010.01.023

[18] Winkley K, Sallis H, Kariyawasam D et al. Five-year follow-up of a cohort of people with their first diabetic foot ulcer: the persistent effect of depression on mortality. Diabetologia 2012; 55:303-310. https://doi.org/10.1007/s00125-011-2359-2

[19] Siersma V, Thorsen H, Holstein PE et al. Health-related quality of life predicts major amputation and death, but not healing, in people with diabetes presenting with foot ulcers: the Eurodiale study. Diabetes Care 2014; 37:694-700. https://doi.org/10.2337/dc13-1212

Figure Legends:

Figure 1: Study Flow Chart

Figure 2 : Kaplan Meier curve of survival, overall (a) and according to PEDIS Perfusion (b). Estimate rate [95% CI]

Figure 1

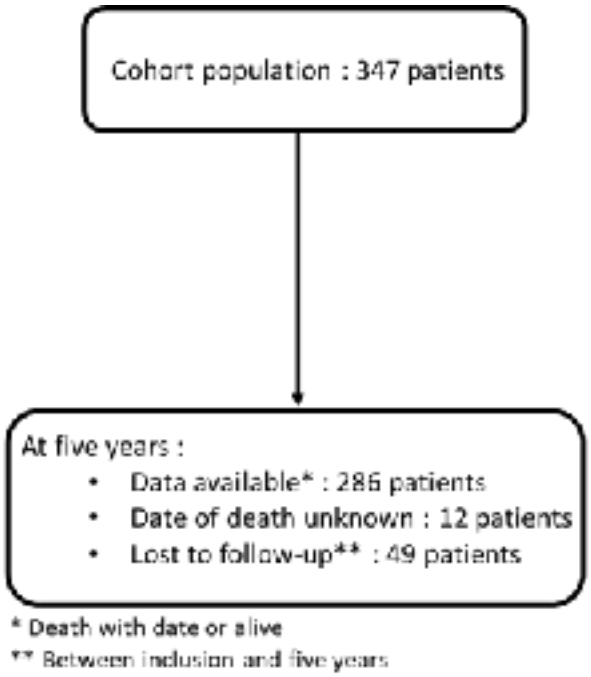
Cohort population : 347 patients
At five years :
Data available* : 286 patients
Date of death unknown : 12 patients
Lost to follow-up** : 49 patients
* Death with date or alive
** Between inclusion and five years

Figure 2

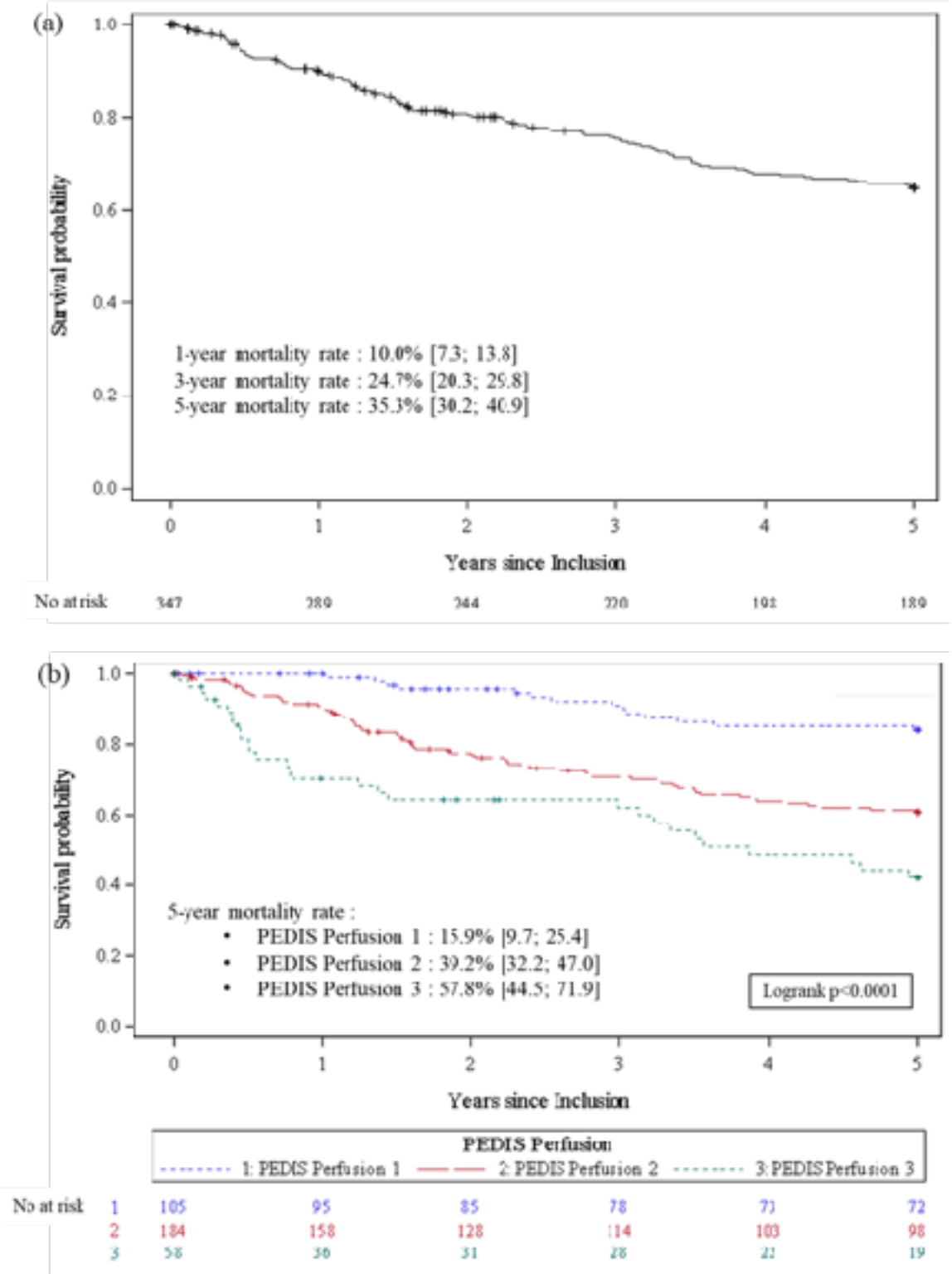
(a)
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
1-year mortality rate : 10.0% [7.3; 13.8]
3-year mortality rate : 24.7% [20.3; 25.8]
5-year mortality rate : 35.3% [30.2; 40.9]
0
1
2
3
4
5
Years since Inclusion
No at risk
347
289
244
220
192
189
(b)
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
5-year mortality rate :
• PEDIS Perfusion 1 : 15.9% [9.7; 25.4]
• PEDIS Perfusion 2 : 39.2% [32.2; 47.0]
• PEDIS Perfusion 3 : 57.8% [44.5; 71.9]
Logrank p<0.0001
0
1
2
3
4
5
Years since Inclusion
PEDIS Perfusion
1: PEDIS Perfusion 1
2: PEDIS Perfusion 2
3: PEDIS Perfusion 3
No at risk
1 105 95 85 78 73 72
2 184 158 128 114 103 98
3 58 36 31 28 22 19

Table 1. Baseline characteristics of patients (n=347

		number of missing observations
Age (year)	65 +/- 12	**0**
Men (%)	237 (68.3)	**0**
BMI (kg/m2)	**28.5 +/- 6.0**	**22**
Active smoking (%)	48 (**14.4**)	**13**
Do not live alone (%)	**256 (76.9)**	**14**
Dialysis (%)	44 (**12.7**)	**0**
Type 2 diabetes (%)	308 (**89.0**)	**1**
Duration of diabetes (years)	19 +/- 12	**4**
Insulin treatment (%)	245 (**71.4**)	**4**
Duration of foot ulcer (days)	49 [19; 120]	**3**
Acute hospitalization at baseline (%)	154 (**50.2**)	**40**
PEDIS Perfusion (%)		**0**
1	**105 (30.3)**	
2	**184 (53.0)**	
3	**58 (16.7)**	
PEDIS Sensation (%)		**0**
1	**58 (16.7)**	
2	**259 (74.6)**	
3	**30 (8.6)**	
TEXAS Classification (%)		**0**
A	**87 (25.1)**	
B	**50 (14.4)**	
C	**97 (28.0)**	
D	**113 (32.6)**	

Data are expressed as mean +/- SD, median [Q1; Q3] or N (%)
* Kaplan-Meier estimate [95% CI]

Table 2: Predictors of five-year mortality

Factors	Univariate analysis HR [95% CI] p-value	Multivariate analysis* aHR [95% CI] p-value
Age (per additional year)	1.06 [1.04; 1.08] <0.001	1.05 [1.03; 1.07] <0.001
Sex (female vs. male)	1.16 [0.78; 1.72] 0.469	
Ulcer duration at baseline (per additional day)	0.999 [0.998; 1.00] 0.037	
BMI (kg/m²) (per additional unit)	0.97 [0.93; 1.00] 0.071	
Do not live alone **(vs. live alone)**	1.17 [0.73; 1.87] 0.515	
Type 2 diabetes	1.24 [0.67; 2.32] 0.496	
Insulin treatment	1.29 [0.84; 1.995] 0.251	
Duration of diabetes (per additional year)	1.02 [1.003; 1.03] 0.021	**1.02 [1.001; 1.03]** **0.032**
Hemodialysis	1.75 [1.05; 2.90] 0.031	
Active smoker	0.79 [0.43; 1.44] 0.433	
PEDIS Perfusion 1 2 3	<0.001 1.00 3.02 [1.70; 5.38] <0.001 5.47 [2.89; 10.35] <0.001	**0.004** **1.00** **2.35 [1.28; 4.29]** **0.006** **3.14 [1.58; 6.24]** **0.001**
PEDIS Sensation 1 2 3	0.030 **1.00** 1.30 [0.78; 2.19] 0.319 0.30 [0.09; 1.01] 0.525	
TEXAS Classification A B C D	<0.001 1.00 0.81 [0.33; 2.01] 0.649 3.20 [1.75; 5.85] <0.001 2.75 [1.51; 5.01] 0.001	

Acute hospitalization **at baseline**	1.03 [0.69; 1.55] 0.878	
Ulcer duration during the first year of follow up**	2.04 [1.37; 3.0.] <0.001	**2.09 [1.35; 3.22]** **<0.001**

*** N=319**

****** time-dependent covariate

aHR : adjusted Hazard Ratio