Diabetes, Lower-Extremity Amputation, and Death

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OBJECTIVE

The goal of the study was to determine whether complications of diabetes well-known to be associated with death such as cardiovascular disease and renal failure fully explain the higher rate of death in those who have undergone a lower-extremity amputation (LEA).

RESEARCH DESIGN AND METHODS

This was a longitudinal cohort study of patients cared for in the Health Improvement Network. Our primary exposure was LEA and outcome was all-cause death. Our "risk factor variables" included a history of cardiovascular disease (a history of myocardial infarctions, cerebrovascular accident, and peripheral vascular disease/arterial insufficiency), Charlson index, and a history of chronic kidney disease. We estimated the effect of LEA on death using Cox proportional hazards models.

RESULTS

The hazard ratio (HR) for death after an LEA was 3.02 (95% CI 2.90, 3.14). The fully adjusted (all risk factor variables) LEA HR was diminished only by ∼22% to 2.37 (2.27, 2.48). Furthermore, LEA had an area under the receiver operating curve (AUC) of 0.51, which is poorly predictive, and the fully adjusted model had an AUC of 0.77, which is better but not strongly predictive. Sensitivity analysis revealed that it is unlikely that there exists an unmeasured confounder that can fully explain the association of LEA with death.

CONCLUSIONS

Individuals with diabetes and an LEA are more likely to die at any given point in time than those who have diabetes but no LEA. While some of this variation can be explained by known complications of diabetes, there remains a large amount of unexplained variation.

Worldwide, every 30 s, a limb is lost to diabetes (1,2). Nearly 2 million people living in the U.S. are living with limb loss (1). According to the World Health Organization, lower-extremity amputations (LEAs) are 10 times more common in people with diabetes than in persons who do not have diabetes. In the U.S. Medicare population, the incidence of diabetic foot ulcers is ∼6 per 100 individuals with diabetes per year and the incidence of LEA is 4 per 1,000 persons with diabetes per year (3). LEA in those with diabetes generally carries yearly costs between $30,000 and $60,000 and lifetime costs of half a million dollars (4). In 2012, it was estimated that those with diabetes and lower-extremity wounds in the U.S. Medicare program accounted for $41 billion in cost, which is ∼1.6% of all Medicare health care spending (4–7). In 2012, in the U.K., it was estimated that the National Health Service spent between

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£639 and 662 million on foot ulcers and LEA, which was approximately £1 in every £150 spent by the National Health Service (8).

LEA does not represent a traditional medical complication of diabetes like myocardial infarction (MI), renal failure, or retinopathy in which organ failure is directly associated with diabetes (2). An LEA occurs because of a disease complication, usually a foot ulcer that is not healing (e.g., organ failure of the skin, failure of the biomechanics of the foot as a unit, nerve sensory loss, and/or impaired arterial vascular supply), but it also occurs at least in part as a consequence of a medical plan to amputate based on a decision between health care providers and patients (9,10). Many researchers have reported a large increase in the incidence of death among LEA patients. The surgical procedure itself is associated with a risk of death that is based on the American Society of Anesthesiologist physical status classification system and is not dependent on risks inherent to the procedure. However, 30-day postoperative mortality can approach 10%, with most mortality associated with those receiving an LEA as an emergency procedure or with the presence of preoperative sepsis (11,12). Previous reports have estimated that the 1-year post-LEA mortality rate in people with diabetes is between 10 and 50%, and the 5-year mortality rate post-LEA is between 30 and 80% (4,13–15). More specifically, in the U.S. Medicare population mortality within a year after an incident LEA was 23.1% in 2006, 21.8% in 2007, and 20.6% in 2008 (4). In the U.K., up to 80% will die within 5 years of an LEA (8). In general, those with diabetes with an LEA are two to three times more likely to die at any given time point than those with diabetes who have not had an LEA (5). For perspective, the 5-year death rate after diagnosis of malignancy in the U.S. was 32% in 2010 (16).

Evidence on why individuals with diabetes and an LEA die is based on a few mainly small (e.g., $<$300 subjects) and often single center–based (13,17–20) studies or $<$1 year duration of evaluation (11). In these studies, death is primarily associated with a previous history of cardiovascular disease and renal insufficiency, which are also major complications of diabetes; these complications are also associated with an increased risk of LEA. The goal of our study was to determine whether complications of diabetes well-known to be associated with death in those with diabetes such as cardiovascular disease and renal failure fully explain the higher rate of death in those who have undergone an LEA.

RESEARCH DESIGN AND METHODS

This is a cohort study of patients from The Health Improvement Network (THIN). THIN data source contains anonymized data collected from the electronic medical records used by General Practice (GP) physicians in the U.K. This data source was chosen because diabetes is a chronic illness. THIN is rich in prospectively collected primary care medical information and has been used in the past to study diabetes and chronic wounds (21–24). Ethics approval for this study was from the Scientific Review Committee U.K. and from the institutional review board from the University of Pennsylvania.

Inclusion Criteria

All individuals were cared for by a GP whose practice was up to THIN standards for data collection and contributed information to THIN during the years 2003–2012. All subjects had diabetes and at least 1 year of follow up and were at least 25 years of age at the time of diagnosis with diabetes. The diabetes diagnosis was based on previously used coding algorithm(s) and has a positive predictive value of 98% (24–26). In addition, for ensuring that all subjects had diabetes, they had to have had at least two visits for diabetes at least 2 months apart. Our primary exposure of interest was any LEA. An LEA was thought to be incident if it was not preceded by a code for LEA in the previous 6 months. Because we were interested in death associated with LEA, any individual who died within the first 2 weeks of the procedure were excluded from study, as their death was thought to be due to preexisting sepsis or due to the surgical event itself. Because it can be difficult to ascertain whether repeated codes for LEA are reporting a new LEA or previous LEA, our primary evaluation of the time to death was from the patient's first LEA. Because coding for LEA can be very broad or quite specific, our primary analysis was based on any code for LEA. However, we also conducted additional analyses using codes for "major amputation" (defined as transtibial or higher). Our coding algorithms have previously been described and implemented (27).

Additional Study Variables

The outcome of interest was all-cause death. Our primary clinical risk factors of interest were selected a priori because they were known to be associated with the most frequent causes of death in those with diabetes. Many of these risk factors are also known to be associated with an increased risk of LEA. Our primary "risk factor variables" included a history of cardiovascular disease such as a history of MI, cerebrovascular accident (CVA), congestive heart failure (CHF), and peripheral vascular disease/arterial insufficiency (PVD); the Charlson comorbidity index (an index that is used to predict mortality); and a history of chronic kidney disease (CKD) as determined by estimate glomerular filtration rate. Coding algorithms for these risk factors have previously been reported (21,24,25,28). We also evaluated a history of malignancy, history of cigarette smoking, sex, HbA_{1c}, and age over 65 years. In addition, we accounted for practice-level variability.

Analysis

The goal of this study was to determine whether complications of diabetes known to be associated with death in those with diabetes, such as cardiovascular disease and renal failure, fully explain the higher rate of death in those who have undergone an LEA. All variables were first evaluated descriptively in the full diabetes cohort, among those with LEA, and among those who died. We then created explanatory models to estimate the effect of LEA on death using Cox proportional hazards models, allowing the effect of LEA to be time varying. In all models, death was our primary outcome and LEA was the primary exposure. Additional covariates and potential confounders were added to the model to determine whether they diminished the effect of LEA on death (29).

We hypothesized that, since LEA is a treatment on the causal pathway to death, the pathway was initiated by another medical risk factor. We therefore

expected that when these "risk factor" variables were added to the proportional hazard models, the association of LEA with death would be diminished (i.e., the hazard ratio [HR] would move toward 1). We hypothesized that this statistical process would show that LEA was a surrogate marker for these other factors that were already known to be the most frequent causes of death in those with diabetes. This analysis was modeled after a conceptual framework developed by Prentice (29). In his classic description of a surrogate marker, Prentice proposed that a true surrogate must yield a valid test of the null hypothesis of no association (i.e., HR = 1) between the treatment and the true response (29). In our setting, the treatment is LEA and the outcome is death. To simplify, we hypothesized that known risk factors for death in those with diabetes, like a history of MI (i.e., the leading cause of death in those with diabetes), should be able to fully explain the association of LEA with death. Since many of these risk factors are also predictors of LEA, many of these associations may also represent confounding, which is often thought to be statistically important if it changes the primary variable's effect estimate by >10–15% (7).

We report HRs for each variable with respect to all-cause death (i.e., unadjusted models), for LEA by itself, and individually with each covariate (i.e., LEA and an additional variable) and for all covariates together (i.e., a fully adjusted model). The proportionality assumption was examined using diagnostic complimentary log-log plots. The fully adjusted Cox models were also evaluated for their ability to predict death using the area under the receiver operator curve (AUC), a statistic often used to describe the ability of a model to discriminate. Finally, sensitivity analyses were performed to determine the magnitude of an unknown risk factor that would be needed to render our findings no longer significant (30). Analyses were conducted using STATA 13.1 and R 3.3.0.

RESULTS

Between 2003 and 2012, 416,434 individuals met the entrance criteria for the study. This cohort accrued an average of 9.0 years of follow-up and a total of 3.7 million diabetes person-years of follow-up. During this period of time, 6,566 (1.6%) patients had an LEA and 77,215 patients died (18.5%). Additional demographic information is reported in Table 1. Nearly all of the risk factors were statistically significantly different with respect to those who had an LEA versus those who did not and those who died versus those who did not (Table 1). The percentage of individuals who died within 30 days, 1 year, and by year 5 of their initial code for an LEA was 1.0%, 9.9%, and 27.2%, respectively. For those >65 years of age, the rates were 12.2% and 31.7%, respectively. For the full cohort of those with diabetes, the rate of death was 2.0% after 1 year of follow up and 7.3% after 5 years of follow up. In general, those with an LEA were more than three times more likely to die during a year of follow-up than an individual with diabetes who had not had an LEA.

From 2003 to 2012, the HR for death after an LEA was 3.02 (95% CI 2.90, 3.14). The HRs for the potential risk factors are presented in Table 2. With respect to death, two other risk factors had HRs similar to LEA: CHF (3.11 [95% CI 3.04, 3.18]) and age >65 years (3.58 [3.52, 3.64]). As noted above, our a priori assumption was that the HR associating LEA with death would be fully diminished (i.e., it would become 1) when adjusted for the other risk factor variables. However, the fully adjusted LEA HR was diminished only ~22% to 2.37 (95% CI 2.27, 2.48). With the exception of age >65 years, individual risk factors, in general, had minimal effect (<10%) on the HR of the association between LEA and death (Table 3). This was also true for clinical practice (data not shown). Furthermore, we estimated the HRs of each of our risk factors just among those who had an LEA in order to evaluate their effect among those with an LEA. In general, the effect estimates for each risk factor were diminished in the LEA cohort compared with the cohort of patients with diabetes (Table 2). A similar finding was noted if we limited our analysis to just those who had documentation of a major LEA (Table 2). With respect to the ability of our models to predict death, a model just containing LEA had an AUC of 0.51, which is poorly predictive (Table 3). As would be expected, the best predictors were older age and the Charlson index (Table 3). Our fully adjusted model had a moderate AUC of 0.76.

We conducted sensitivity analyses to determine the general statistical parameters of an unmeasured risk factor that could remove the association of LEA with death. We found that even if there

Table 1—Important demographic and risk factor variables for the cohort of individuals with diabetes and the subcohorts of individuals who had an LEA and those who died

	Full cohort	LEA subgroup	Those who died
Age >65 years	38.9	36.7#	63.8*
Male sex	54.3	68.1*	53.0*
HbA_{1c} (%)			
<7	49.2	40.2	52.7
7–9	35.6	36.4	32.7
>9	15.2	23.5*	14.6*
CKD category			
1	88.3	81.7	76.5
2	10.8	15.8	21.1
3	0.83	2.56*	2.35*
Charlson	0.76 (1.4)	0.96 (1.4)*	1.61 (1.9)*
MI	10.3	19.6*	19.9*
CVA	9.3	17.4*	18.4*
PVD	4.3	31.8*	9.2*
CHF	3.5	7.8*	10.9*
Malignancy	12.1	12.4	24.75*
Cigarette use			
Never smoked	42.3	37.1	43.3
Past smoker	41.4	44.5	41.1
Current smoker	16.3	18.4*	15.6

Data are percent or mean (SD). *$P < 0.0001$; #$0.0001 < P < 0.001$.

Table 2—Unadjusted and fully adjusted HRs (95% CI)

Covariate	Full cohort (unadjusted)	Full cohort (adjusted)	LEA subgroup (unadjusted)	Major LEA subgroup (unadjusted)
LEA	3.02 (2.90, 3.14)	2.37 (2.27, 2.48)		
Age >65 years	3.58 (3.52, 3.64)	2.62 (2.57, 2.67)	1.43 (1.32, 1.54)	1.31 (1.17, 1.47)
CKD				
1	ref.	ref.	ref.	ref.
2	2.23 (2.20, 2.27)	1.48 (1.45, 1.51)	1.41 (1.29, 1.55)	1.25 (1.08, 1.45)
≥3	2.80 (2.67, 2.94)	2.02 (1.91, 2.13)	1.90 (1.54, 2.34)	1.64 (1.18, 2.28)
Charlson	1.29 (1.29, 1.29)	1.17 (1.16, 1.18)	1.10 (1.08, 1.13)	1.07 (1.04, 1.11)
MI	1.85 (1.81, 1.88)	1.37 (1.35, 1.40)	1.53 (1.40, 1.67)	1.43 (1.28, 1.65)
CVA	1.92 (1.88, 1.95)	1.34 (1.31, 1.37)	1.34 (1.22, 1.47)	1.22 (1.07, 1.39)
PVD	1.62 (1.58, 1.66)	1.13 (1.10, 1.16)	1.72 (1.59, 1.86)	1.31 (1.17, 1.47)
CHF	3.11 (3.04, 3.18)	1.39 (1.35, 1.44)	1.98 (1.77, 2.22)	1.73 (1.47, 2.05)
Cigarette use				
Never smoked	ref.	ref.	ref.	ref.
Past smoker	0.97 (0.95, 0.98)	0.91 (0.90, 0.93)	0.84 (0.76, 0.91)	0.75 (0.66, 0.87)
Current smoker	1.08 (1.06, 1.11)	1.34 (1.31, 1.38)	0.89 (0.79, 1.00)	0.84 (0.71, 0.99)
HbA_{1c} (%)				
<6	ref.	ref.	ref.	ref.
>6–9	0.56 (0.55, 0.57)	0.68 (0.66, 0.69)	0.98 (0.89, 1.08)	0.93 (0.80, 1.07)
>9	0.54 (0.52, 0.55)	0.71 (0.69, 0.73)	1.19 (1.07, 1.33)	1.19 (1.01, 1.40)
Malignancy	2.39 (2.35, 2.43)	1.34 (1.31, 1.37)	1.15 (1.03, 1.28)	1.00 (0.84, 1.18)
Male	0.95 (0.93, 0.96)	1.07 (1.05, 1.09)	1.02 (0.94, 1.11)	1.15 (1.02, 1.31)

Fully adjusted HRs (LEA, age >65 years, CKD, Charlson index, MI, CVA, PVD, CHF, cigarette use, HbA_{1c}, malignancy, and sex). Unadjusted HRs are also reported for the subcohorts of individuals who had an LEA and for those who had a major LEA. ref., reference category.

existed a very strong risk factor with an HR of death of three, a prevalence of 10% in the general diabetes population, and a prevalence of 60% in those who had an LEA, LEA would still be associated with a statistically significant and clinically important risk of 1.30. These findings are describing a variable that would seem to be so common and so highly associated with death that it should already be clinically apparent. We also conducted sensitivity analysis excluding individuals who died within the first 30 days after their LEA. These sensitivity analyses also included adjustment for measurements of total cholesterol and LDL and HDL (which were only available for ~65% of the population) and blood pressure. These secondary sensitivity analyses demonstrated very minimal effects on the adjusted effect estimate between LEA and all-cause death as noted in Table 2.

Table 3—HRs (95% CI) for LEA after adjustment for the listed covariate

Covariate	Full cohort	AUC
LEA		0.512
Age >65 years	2.64 (2.54, 2.74)	0.669
CKD	2.88 (2.77, 2.99)	0.581
Charlson	2.81 (2.71, 2.92)	0.693
MI	2.91 (2.80, 3.02)	0.566
CVA	2.88 (2.77, 2.99)	0.564
PVD	2.78 (2.67, 2.89)	0.532
CHF	2.88 (2.78, 3.00)	0.555
Cigarette use	3.03 (2.91, 3.16)	0.511
HbA_{1c}	2.97 (2.85, 3.10)	0.535
Malignancy	2.93 (2.82, 3.04)	0.589
Male	3.05 (2.93, 3.17)	0.524

AUC for these two variable models is also listed. As a frame of reference, the HR for the unadjusted model containing the LEA covariate is 3.02 (2.90, 3.14), and the AUC for the fully adjusted model is 0.763.

CONCLUSIONS

This is the largest and longest evaluation of the risk of death among those with diabetes and LEA. Individuals in the U.K. treated by a health care provider who participates in THIN with diabetes who have had an LEA are three times more likely to die at any point in time than their counterparts who have not had an LEA. In any given year, >5% of those with diabetes and an LEA will die. The goal of this study was to determine whether complications of diabetes well-known to be associated with death in those with diabetes, like cardiovascular disease and renal failure, explained the higher rate of death among those who have undergone an LEA. It is important to understand whether these factors increase the risk of death in those who have had an LEA. LEA is a procedure, and many receiving this procedure will also have these medical conditions. Many of these conditions are also associated with the reason for the LEA such as severe PVD and therefore are associated with both the procedure and, potentially, death. The surgical procedure by itself is unlikely to contribute to a patient's risk of dying. We were not able to demonstrate that the increased risk of death in those with diabetes and an LEA was primarily explained by MI, CKD, CVA, CHF, PVD, or a previously validated mortality index, the Charlson index. Furthermore, we were able to show that to fully explain the association between death and LEA, we would need to hypothesize a risk factor that is very highly associated with death and very common—a risk factor that one might imagine should already be known.

The indication for an LEA is as variable as is the procedure itself (e.g., the part of the lower extremity removed). Recently, it was reported that the annual incidence of LEA is between 4 to 5 per 1,000 person-years in 5 million beneficiaries with diabetes in the U.S. Medicare population between 2006 and 2008 (14). There was also a three- to fivefold geographic variation in amputation incidence (14).

Similarly, a study in 2012 by Holman et al. (27) demonstrated an incidence of LEA in those with diabetes of ~2.5 per 1,000 person-years and also noted an eightfold geographic variation in LEA rates among the Primary Care Trusts in England.

Death from anesthesia during the performance of an LEA is very uncommon, and it is similar to the risk of death from anesthesia for a person of similar medical health. Previous studies on why LEA is associated with high mortality found associations similar to ours. A study from Zambia from 2003 showed that 55% of those with LEA and PVD died within 5 years of their LEA (19). A study of 390 individuals form Scotland in 2006 of individuals with nontraumatic LEA showed that those with diabetes and CHF were the most likely to die within a year of surgery (20). A study of 38 subjects with diabetes and amputation from Germany demonstrated that older age, renal insufficiency, and PVD were all associated with an increased risk of death (18). A study in 2012 from the U.S. Veterans Administration system showed that those with CVA and those who had intensive care unit stays during their admission for LEA had an increased risk of death (31). A small study of 93 individuals who had a nontraumatic amputation from Denmark in 2012 showed that individuals with diabetes, vascular disease, and more severe systemic illnesses were more likely to die within the first year postamputation (32). A study from the Netherlands in 2013 of 299 patients with diabetes and LEA revealed that renal disease and cerebrovascular disease were associated with an increased risk of death (17). Our study is larger, includes longer follow-up, evaluates those with LEA to those without over time, and was from a database that is thought to be highly representative of the U.K.

LEA is often performed because of an end-stage disease process like chronic nonhealing foot ulcer. By the time a patient has a foot ulcer and an LEA is offered, they are likely suffering from the end-stage consequence of diabetes. A recent study indicated that the 30-day mortality rate after LEA was 7.1% (12). This number included all individuals receiving an LEA and was not specific to patients with diabetes. The majority of the cases who died had sepsis, again demonstrating that this procedure is reserved for individuals who are critically ill. Because we were interested in long-term mortality and not that associated with the immediate surgical intervention, we excluded from our analyses those who died within the first 2 weeks after their LEA. However, a possible explanation for our findings and the previous findings of regional variation is that the selection of whom to offer an LEA is biased to those who are significantly ill and have marked increased risk of mortality compared with others with diabetes. This unmeasured bias is significant, not represented in the Charlson index, and likely clinically obvious to those making the treatment selection.

As with all epidemiologic studies, our study has several potential limitations. We used the THIN database. It is possible that we missed patients with diabetes who had an LEA. This is unlikely in that our rates of diabetes are similar to those of other U.K. studies (33). It is important to remember that the GPs who recorded clinical information in THIN were unlikely to have performed the LEA. As a result, it is possible that patients could have died, which would have been recorded in THIN, just after their LEA in hospital without receiving care by their GP postsurgery, thereby resulting in the failure to record the LEA in THIN. These individuals would have contributed to deaths in our individuals with diabetes who did not have an LEA, thereby biasing our results toward the null. Immortal time bias can occur in longitudinal studies of treatment interventions. However, to control for this form of bias, we allowed LEA to be a time-varying covariate. With respect to other forms of bias like information bias, others have demonstrated the accuracy of THIN in the past (34). In large studies like this one, most information bias tends to be nondifferential. There is no reason to suspect that among individuals with diabetes, important factors like cardiovascular illness or renal failure would be more accurately reported depending on whether an LEA was going to happen in the future. It is also important to realize that we focused on all-cause mortality and while we focused on risk factors that are consistent with cardiovascular complications of diabetes and thus associated with cardiovascular-associated death, we did not evaluate modifiable risk factors like lipids and blood pressure. For ~65% of our population, we did have data on total cholesterol, HDL, LDL, and blood pressure. We did conduct a secondary analysis on these subjects, which was not formally reported, but it did not have an effect on the multivariate HR reported in Table 2 for LEA and all-cause death. It is also important to realize that in this study we focused on all-cause death and not the cause of death. Cause of death is difficult to properly determine in THIN. Finally, generalizability is always a concern. THIN is thought to represent the U.K. population. The LEA rate is somewhat lower than in the U.S., but as long as the effect ratios of those with and without LEA are consistent across populations our results should generalize outside of the U.K.

In summary, individuals with diabetes and an LEA are more likely to die at any given point in time than those who have diabetes but no LEA. While some of this variation can be explained by other known complications of diabetes, the amount that can be explained is small. Based on the results of this study, including a sensitivity analysis, it is highly unlikely that a "new" major risk factor for death exists. It is possible that the risk of death is related to those being selected for LEA, which is a procedure commonly viewed as a last effort to treat a patient's foot ulcer. However, it is likely that the major causes of death in those with diabetes and LEA is similar to the causes in those who have not had an LEA (e.g., MI, CVA, CHF, CKD, etc.) (35). If this were true, then based on our results GPs could be failing to evaluate those with an LEA for these medical conditions or, as others have opined, the diagnosis of these conditions in those with LEA might be different as well as the pathophysiology of cardiovascular disease and its relationship with all-cause death (35). We would therefore suggest that patients who have had an LEA require even more vigilant follow-up and evaluation to assure that their medical care is optimized. It is also important that GPs communicate to their patients about the risk of death to assure that patients have proper expectations about the severity of their disease.

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Author Contributions. O.H. and D.J.M. designed the study and obtained the data. O.H., N.M., J.W., and D.J.M. conducted statistical

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