Postoperative Death After Lower-Limb Amputation in a National Prevalent Cohort of Patients With Diabetes

Jason K. Gurney,[1] James Stanley,[1] Juliet Rumball-Smith,[2] Steve York,[2] and Diana Sarfati[1]

Diabetes Care 2018;41:1204–1211 | https://doi.org/10.2337/dc17-2557

EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

The objectives of this study were to *1*) describe postoperative mortality after lower-limb amputation in a national prevalent cohort of patients with diabetes, and *2*) investigate whether postoperative mortality differs by demographic subgroup, patient morbidity level, and health system factors related to the facility in which the amputation occurred.

RESEARCH DESIGN AND METHODS

A national prevalent cohort of 302,339 individuals diagnosed with diabetes between 2005 and 2014 was followed until the end of 2014 for major and minor lower-limb amputation and subsequent postoperative mortality by using national health data collections. Kaplan-Meier survival analysis was used to determine postoperative survival, whereas Cox proportional hazards models were used to describe the relative hazard of postoperative mortality, adjusted for covariates.

RESULTS

A total of 6,352 lower-limb amputations occurred over the study period (2,570 major amputations, 3,782 minor amputations). More than 11% of patients who underwent major amputation died within 30 days, whereas nearly 18% died within 90 days. Death was most common among older patients and indigenous Māori. Sex, deprivation, rurality, hospital volume, admission type, and patient comorbidity were not consistently or substantially independently associated with risk of postoperative mortality.

CONCLUSIONS

In a national prevalent cohort of patients with diabetes, there was high risk of postoperative mortality as well as a differential risk of postoperative mortality by demographic subgroup. Further work is required to investigate the drivers of postoperative mortality among patients with diabetes who undergo amputation.

Although the exception rather than the norm, death in the days and weeks immediately after a surgical procedure is not uncommon (1). In a U.S. study of >360,000 patients who underwent procedures between 2005 and 2007, a 30-day mortality rate of 1.75%, or 6,395 deaths, was observed (2). Nearly one-quarter of all postoperative deaths occur after the patient has been discharged from the hospital (2).

When examining postoperative mortality, a threshold of 30 days after surgery is a valid and meaningful measure (3–5) for two key reasons. First, a 30-day threshold is

[1]Cancer and Chronic Conditions Research Group, Department of Public Health, University of Otago, Wellington, New Zealand
[2]Northland District Health Board, Whangarei, New Zealand

Corresponding author: Jason K. Gurney, jason.gurney@otago.ac.nz.

Received 7 December 2017 and accepted 13 March 2018.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-2557/-/DC1.

This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

less influenced by events that take place during or immediately after surgery and will include the impact of postoperative care in the weeks after the procedure (3,4). Second, because postoperative infections typically occur within 28 days of surgery, a 30-day threshold allows for the life course of these infections (1).

Lower-limb amputation is one of the most serious surgical procedures performed in patients with diabetes. Patients with diabetes are more likely to require lower-limb amputation than people without diabetes (6–9). For example, in a French study, the incidence of amputation was 12 times higher among patients with diabetes than among those without diabetes (9).

Evidence shows that patients with diabetes who undergo lower-limb amputation have a high mortality rate (10–16). However, most investigations since have either focused on comparing rates between diabetic and nondiabetic populations (10,12,13,17–19), only investigated long-term outcomes (12,20), or restricted analyses to subgroups of the diabetic population (20) or to single hospitals (21). A paucity of large studies have investigated mortality immediately after amputation in a well-defined diabetic population, and as such, gaps exist in our understanding of the frequency of postoperative mortality in this population, how postoperative mortality differs within this population, and the factors that ultimately drive this outcome.

The objectives of this article are to describe postoperative mortality after lower-limb amputation in a large cohort of patients with diabetes and then to investigate whether postoperative mortality differs by *1*) population demographic factors, *2*) health system factors, and *3*) patient-level factors related to comorbidity.

RESEARCH DESIGN AND METHODS

Patients and Data Sources

The national prevalent cohort of New Zealand patients with diabetes diagnosed between 2005 and 2014 (N = 302,339), determined from the Ministry of Health Virtual Diabetes Register (VDR), was used for this study. This register uses multiple informant databases to define the presence of diabetes in a given individual, including hospital discharge, outpatient, national pharmaceutical, and laboratory data (Supplementary Material 1). The Ministry of Health uses the VDR to estimate annual diabetes prevalence in New Zealand (22). All cohort patients in the register were assumed to have diabetes.

After the study cohort was defined by using the VDR, we linked individual patients to inpatient hospital discharge data, starting from the year 2000 through to 2014 (the National Minimum Dataset [NMDS]). The NMDS includes diagnosis and procedure codes in ICD-10 format, which were used to define patient comorbidity and the occurrence of amputation (see VARIABLES).

Finally, we linked the study cohort to the national mortality data collection from 2005 to 2014 to define the occurrence of death within the postoperative period. We used 30-day mortality as our primary outcome and included 90-day mortality as a secondary outcome.

Variables

For each patient, we searched the NMDS for amputation procedures that occurred between 2005 and 2014 by using ICD-10 procedure codes (Supplementary Material 3). Amputations were categorized as either major (above or through the ankle) or minor (below the ankle) (23). If a given amputation event included both a major and a minor amputation, only the major amputation was retained (n = 358 occurrences [i.e., 14% of all major amputations were accompanied by a minor amputation on the same day]). It was possible for patients to appear more than once in our data set if they had more than one amputation event during the follow-up period (e.g., a minor amputation in 2005 and a major amputation in 2010).

We scanned the list of amputations for those that had an accompanying trauma code during the given hospitalization event, indicating that the amputation may have been related to a trauma event (ICD-10 codes S78, S88, S98, T053–6, T136). Of all the amputation events that occurred over the follow-up period, only seven were flagged as related to trauma (0.1% of events). Given this small number of events and the possibility that these trauma-related amputations were at least partially related to the patient's diabetes, these amputations were retained in the analysis.

Patient sex, ethnicity, deprivation, and rurality were determined from the VDR data set. Patient ethnicity was categorized as either Māori (the indigenous population of New Zealand), Pacific (Samoan, Cook Island Māori, Tongan, Niuean, Tokelauan, Fijian, or other Pacific), Asian (Southeast Asian, Chinese, Indian, or other Asian) or non-Māori/non-Pacific/non-Asian (referred to as European/other) (24). Patient deprivation was defined by using the 2013 New Zealand Index of Deprivation (NZDep) quintiles. NZDep uses multiple informant variables to define the level of deprivation for a given area (25). Missing data prevented the attribution of deprivation for 2,584 patients (0.8% of the total cohort). We classified patient rurality by using a modified version of the Urban/Rural Profile Classification (URPC) (26) to define census areas as either urban, independent urban, or rural. Missing data prevented the attribution of rurality for 2,763 patients (0.9% of the cohort). Patient age was determined separately for each amputation event and was defined by subtracting the patient's date of birth from the date of amputation. Patient age was categorized as either $<$25, 25–49, 50–64, 65–74, or $\geq$75 years.

Hospital volume was defined by using NMDS data. We looked for all amputations that occurred over the study period and cross-tabulated the number of amputations performed per year by each hospital. On the basis of this cross-tabulation, we were able to establish that hospitals largely clustered into three groups: those that performed $>$500 amputations per year (high volume), those that performed 100–499 amputations per year (medium volume), and those that performed $<$100 amputations per year (low volume).

Admission type was defined by using NMDS data. This variable is recorded in hospitalization discharge records as either acute, arranged/privately funded elective, or waiting list admission. For the purposes of this study, we defined admission type as either acute or nonacute (i.e., elective).

Risk of mortality associated with patient comorbidity was defined by using the M3 index of multimorbidity (27), which includes 61 long-term conditions that are based on ICD-10 coding (two conditions were not included in our scoring for this analysis: diabetes with complications and diabetes without complications). A full list of conditions is included in Supplementary Material 2 along with the prevalence of each of these conditions within the study cohort. Level of patient comorbidity was determined at each individual

amputation event. We examined the NMDS data in the 5-year period before every amputation to code the presence of each relevant M3 index condition. Each identified condition was then weighted on the basis of the condition's previously determined independent impact on mortality in the general population (described elsewhere [27]), with these weights then summed to arrive at the final M3 index score for a patient at each amputation event. M3 index was then categorized into the following five categories for the purposes of descriptive analysis: 0, >0–1, >1–2, >2–3, and ≥3. For the purposes of Cox proportional hazards modeling, M3 index score was included as a splined linear variable (27), with knots placed at the 10th, 50th, and 90th percentiles (28).

After the final data set was created, we used mortality data to search for deaths that occurred within a 30- and 90-day period after each amputation event. Death date was used to determine survival time for patients who died within this postoperative period.

Statistical Analysis

Descriptive Analysis

We described the crude number of amputation events over the follow-up period by major/minor amputation type, with results stratified by covariates (sex, age, ethnicity, deprivation, rurality, hospital volume, admission type, and comorbidity). We also described the crude number of deaths that occurred within 30 and 90 days of the amputation events.

Survival Analysis

To determine the crude proportion of deaths that occurred within 30 and 90 days of amputation, we used Kaplan-Meier survival analysis. We censored events when either *1*) no death occurred after 30 (or 90) days of follow-up, in which case patients were censored at the end of the respective periods, or *2*) a subsequent amputation occurred within a 30- (or 90-) day period from the date of the original amputation. The latter censoring was performed to ensure that death was only attributed to the amputation that occurred closest in time to the date of death. A total of 280 amputations occurred within 30 days of a previous amputation (4% of all amputations), whereas 797 amputations occurred within 90 days of a previous amputation (13% of all amputations). However, the impact of this censoring was minimal. For example, only seven individuals who died within 30 days of an amputation had had another amputation within the prior 30-day period. In addition to determining the crude proportion of deaths that occurred postamputation, we created Kaplan-Meier curves to compare survival probability over the 90-day period between amputation types.

Cox Proportional Hazards Modeling

We used Cox proportional hazards modeling to compare the instantaneous risk of postoperative mortality within covariate groups. Adjusted models that included sex (reference: female), age (reference: 50–64 years), ethnicity (reference: European/other), deprivation (reference: NZDep quintiles 1–2 [least deprived]), rurality (reference: urban), hospital volume (reference: >500 amputations/year), admission type (reference: elective), and comorbidity (reference: M3 index score 0) were fitted for both amputation types. Final adjusted hazard ratios (HRs) were thus the independent association between the given covariate and risk of postoperative death, adjusted for all other covariates. HRs were only calculated for 30-day mortality to avoid modeling two proportional hazards models that included the same time period with the highest risk of mortality (i.e., the first 30 days after surgery).

Finally, after assessing the results of the crude and adjusted HRs, we selected two key exposure groups (age and ethnicity) and assessed the iterative impact of including each covariate into the Cox models. To do this, we fitted crude models that compared risk of postoperative mortality between *1*) older (≥75 years) versus younger (50–64 years) patients, and *2*) Māori versus European patients. We then added covariates to the model in a step-by-step fashion to assess the impact of each set of factors on relative differences in outcomes. Variables were conceptualized as demographic factors (age, sex, ethnicity, deprivation, rurality), health system factors (hospital volume, admission type), or patient-level factors (comorbidity). Data management and analysis was performed with SAS 9.3 statistical software (SAS Institute) and Microsoft Excel 2010 (Microsoft Corporation).

RESULTS

Characteristics of the cohort are presented in Table 1. Among the 302,339 patients included in the VDR cohort, 6,352 lower-limb amputations were performed over the study period (2,570 major amputations and 3,782 minor amputations) in 4,164 unique individuals.

Numbers and proportions of deaths (the latter determined by using Kaplan-Meier survival analysis) are presented in Table 2, whereas a crude Kaplan-Meier survival curve is presented in Supplementary Material 4. Of the 2,570 major amputations that occurred over the follow-up period, 11.1% (95% CI 10–12.4%) were followed by death within 30 days, and 17.6% (95% CI 16.1–19.1%) were followed by death within 90 days.

Adjusted HRs showing the instantaneous risk of death within 30 days for each covariate by amputation type are presented in Table 3. Male patients had a marginally lower risk of dying after a major amputation than female patients, although the CI included the null (adjusted HR 0.87 [95% CI 0.68–1.11]). In terms of age, the greatest risk of postoperative death was observed among those >75 years of age. Compared with patients 50–64 years of age, this group had a 59% greater risk of death after a major amputation (1.58 [95% CI 1.15–2.18]) and four times the risk after a minor amputation (4.15 [95% CI 2.45–7.03]).

Māori were consistently more likely to die during the postoperative period. Compared with the European/other population, Māori had a nearly 50% greater risk of dying immediately after a major amputation (HR 1.46 [95% CI 1.08–1.98]) as well as a 74% greater risk of dying after a minor amputation (1.73 [95% CI 1.02–2.94]).

No clear evidence showed that level of deprivation independently affected the likelihood of postoperative death. Although patients in the poorest deprivation quintiles appeared to have a greater risk of dying after a minor amputation than those living in the least-deprived quintiles, CIs were wide and included the null (e.g., HR for quintile 1 relative to quintile 5, 1.79 [95% CI 0.81–3.92]). Similarly, although our best estimate was that patients residing in rural areas had a 24% greater risk of dying after a major amputation (1.24 [95% CI 0.82–1.87]) and a 54% greater risk after a minor amputation (1.43 [95% CI 0.84–2.8]) than those living in urban areas, the CIs around these estimates included the null, so we cannot rule out the possibility of no difference in survival by rural status (Table 3).

Table 1—Characteristics of the cohort, by amputation type

	Major amputation		Minor amputation	
	n	%	*n*	%
Total cohort[1]	2,570	—	3,782	—
Sex[2]				
Female	891	34.8	1,147	30.5
Male	1,672	65.2	2,615	69.5
Age-group (years)				
0–24	10	0.4	24	0.6
25–49	236	9.2	456	12.1
50–64	706	27.5	1,166	30.8
65–74	708	27.5	999	26.4
≥75	910	35.4	1,137	30.1
Age (years)[3]	68.7	13	66.6	13.3
Ethnicity				
Māori	665	25.9	632	16.7
Pacific	195	7.6	356	9.4
Asian	62	2.4	103	2.7
European/other	1,648	64.1	2,691	71.2
Deprivation (NZDep)				
1–2 (least deprived)	173	6.8	365	9.7
3–4	293	11.5	457	12.2
5–6	454	17.8	662	17.7
7–8	645	25.3	1,024	27.3
9–10 (most deprived)	984	38.6	1,239	33.1
Rurality (URPC)				
Urban	1,860	73.4	2,681	72.6
Independent urban	480	18.9	660	17.9
Rural	195	7.7	352	9.5
Hospital volume (amputations/year)				
>500	1,525	59.9	2,252	60.7
100–499	830	32.6	1,103	29.8
<100	191	7.5	352	9.5
Admission type				
Acute	1,875	73	2,647	70
Elective	695	27	1,135	30
Comorbidity (M3 index)				
0	280	10.9	425	11.2
>0–1	864	33.6	1,255	33.2
>1–2	883	34.4	1,227	32.4
>2–3	421	16.4	668	17.7
≥3	122	4.7	207	5.5

[1]All amputation events occurred between 2005 and 2014. If an event included both a major and a minor amputation, only the major amputation was counted. [2]Sex data were missing for 27 patients (0.4% of amputation events). [3]Age data are mean and SD.

Acute admission independently conferred a 44% increased risk of mortality after a major amputation (HR 1.44 [95% CI 1.07–1.93]) and a 43% increased risk of mortality after a minor amputation (1.43 [95% CI 0.92–2.22]). However, no consistent evidence shows that the number of amputations performed at a given hospital is related to risk of postoperative mortality. For example, patients who underwent a major amputation seemed to have a similar risk of dying within 30 days whether their hospital performed >500 amputations a year (reference group) or <100 a year (0.86 [95% CI 0.52–1.40]).

Overall comorbidity burden did not appear to substantially increase the risk of postoperative mortality. Although increasing M3 index scores seemed to be associated with increasing risk of postoperative mortality after a major amputation, the CIs were wide and included the null. Comorbidity did not appear to affect risk of mortality after a minor amputation (Table 3).

Results of the two step-by-step regression analyses for age and ethnicity are shown in Table 4. When iteratively introducing covariates into a model comparing the risk of mortality between patients in the oldest age-group (≥75 years) with those in the 50–64-year age-group, we observed that only ethnicity had a discernible impact on this disparity (e.g., major amputation: sex-adjusted HR 1.33, sex- and ethnicity-adjusted HR 1.62, fully adjusted HR 1.59). Similarly, when comparing the risk of postamputation mortality between Māori and European/other patients, we observed that age had the most discernible impact on the disparity (e.g., major amputation: crude HR 1.30, age-adjusted HR 1.58, fully adjusted HR 1.46).

CONCLUSIONS

We observed that >1 of every 10 patients (11%) who underwent a major amputation died within 30 days of their procedure, and >1 in 6 (18%) died within 90 days. Death was less frequent among those who underwent a minor amputation but not insubstantially, with 3% having died within 30 days and 6% within 90 days. Although this rate of postoperative mortality is substantial, it is consistent with other diabetes literature (3,10,12,15–17), including a systematic review of mortality after lower-limb amputation (18).

Although male patients were more likely to require an amputation in the first place, little difference existed between the sexes in terms of adjusted risk of postoperative mortality, consistent with other research (11). This finding suggests that female patients who undergo amputation are similar to their male counterparts in terms of underlying risk factors for postoperative mortality.

Patients in the oldest age-group were at the greatest risk of death for both amputation types and, in relative terms, were at particularly high risk of mortality after a minor amputation. Those ≥75 years of age had four times the risk of dying within 30 days of a minor amputation than those 50–64 years of age. This finding is consistent with other diabetes studies that observed differences in postamputation mortality outcomes between younger and older patients (11), indicating that risk of postoperative mortality is the greatest among the elderly. Amputation procedures undertaken in this group must be well justified on the basis of health need or potential benefit and accompanied by high-quality postoperative care.

Table 2—30- and 90-day mortality by amputation type and further stratified by covariates

	Major amputation				Minor amputation			
	30-day mortality		90-day mortality		30-day mortality		90-day mortality	
	n[1]	% (95% CI)[2]	n[1]	% (95% CI)[2]	n[1]	% (95% CI)[2]	n[1]	% (95% CI)[2]
Total deaths	289	11.1 (10–12.4)	471	17.6 (16.1–19.1)	119	3 (2.5–3.6)	259	5.6 (4.9–6.4)
Sex								
Female	112	12.5 (10.5–14.8)	185	20.2 (17.7–22.9)	37	3.1 (2.3–4.3)	82	5.4 (4.3–6.9)
Male	177	10.5 (9.1–12)	286	16.3 (14.6–18.1)	82	3 (2.4–3.8)	177	5.8 (4.9–6.7)
Age (years)								
0–24	0	0 (0–0)	0	0 (0–0)	0	0 (0–0)	0	0 (0–0)
25–49	23	9.7 (6.6–14.3)	31	13.1 (9.4–18.2)	5	1.1 (0.5–2.6)	15	1.3 (0.6–2.9)
50–64	74	10.3 (8.3–12.8)	113	14.9 (12.5–17.8)	23	1.8 (1.2–2.8)	55	3.5 (2.6–4.8)
65–74	66	9.2 (7.3–11.6)	123	16.4 (13.9–19.4)	30	2.8 (1.9–4)	62	5.4 (4.2–7)
≥75	126	13.7 (11.7–16.1)	204	21.8 (19.3–24.6)	61	5.4 (4.2–6.8)	127	9.8 (8.2–11.7)
Ethnicity								
Māori	88	13.1 (10.8–15.9)	142	17.7 (10.2–29.7)	23	3.5 (2.3–5.2)	50	5.8 (2.7–12.5)
Pacific	20	10.3 (6.7–15.4)	30	16.9 (15.2–18.8)	12	3.4 (1.9–5.9)	21	5.7 (4.9–6.6)
Asian	10	16.1 (9–27.9)	11	20 (17.1–23.2)	3	2.9 (0.9–8.8)	6	5.6 (4–7.7)
European/other	171	10.3 (8.9–11.8)	288	14.9 (10.6–20.7)	81	2.9 (2.3–3.6)	182	5.4 (3.5–8.3)
Deprivation (NZDep)								
1–2	22	12.7 (8.6–18.7)	30	17.3 (12.5–23.9)	9	2.2 (1.1–4.3)	31	6.9 (4.7–10.1)
3–4	28	9.6 (6.7–13.5)	48	15.7 (12–20.5)	7	1.5 (0.7–3.2)	17	2.6 (1.5–4.6)
5–6	51	11 (8.5–14.3)	85	17.7 (14.5–21.6)	19	2.9 (1.8–4.5)	42	5.5 (4–7.5)
7–8	75	11.6 (9.4–14.4)	117	17.3 (14.6–20.4)	37	3.6 (2.6–5)	78	6.6 (5.2–8.3)
9–10	112	11.2 (9.4–13.3)	190	18.6 (16.3–21.1)	47	3.6 (2.7–4.7)	91	5.9 (4.7–7.3)
Rurality (URPC)								
Urban	211	11.3 (9.9–12.8)	336	17.3 (15.7–19.1)	78	2.9 (2.3–3.6)	176	5.4 (4.6–6.3)
Independent urban	48	9.8 (7.5–12.8)	91	18.6 (15.4–22.4)	27	3.8 (2.6–5.6)	53	6.7 (5–8.9)
Rural	28	13.9 (9.7–19.6)	42	19.7 (14.7–26)	14	3.7 (2.2–6.3)	30	7.2 (4.9–10.4)
Hospital volume (amputations/year)								
>500	174	11.3 (9.8–13)	279	17.6 (15.8–19.6)	68	3 (2.4–3.8)	148	5.6 (4.7–6.7)
100–499	95	11.3 (9.4–13.7)	155	17.8 (15.3–20.6)	40	3.4 (2.5–4.7)	94	6.8 (5.4–8.4)
<100	18	9.4 (6–14.5)	35	17.3 (12.7–23.5)	11	2.6 (1.3–4.9)	17	3.4 (2–6)
Admission type								
Acute	231	12.2 (10.8–13.8)	376	19.2 (17.5–21.1)	91	3.3 (2.7–4.1)	192	6 (5.2–7)
Elective	58	8.2 (6.4–10.5)	95	13.1 (10.8–15.9)	28	2.4 (1.6–3.5)	67	4.7 (3.6–6.1)
Comorbidity (M3 index)								
0	31	11.1 (7.9–15.4)	54	18.6 (14.5–23.7)	12	2.6 (1.4–4.6)	21	4.5 (2.9–6.9)
>0–1	91	10.3 (8.5–12.5)	145	15.5 (13.2–18.1)	47	3.7 (2.8–4.9)	96	6.2 (5–7.6)
>1–2	102	11.6 (9.6–13.8)	168	18.7 (16.3–21.5)	34	2.8 (2–3.9)	83	5.7 (4.6–7.2)
>2–3	50	11.6 (8.9–15.1)	77	17.4 (14.1–21.4)	22	3 (1.9–4.6)	45	5.7 (4.2–7.8)
≥3	15	12.3 (7.6–19.6)	27	22.1 (15.7–30.6)	4	1.9 (0.7–5.1)	14	3.9 (2–7.7)

[1]Deaths within 30 (or 90) days of amputation. Deaths in the 90-day columns include those that occurred within 30 days. [2]Determined by using Kaplan-Meier survival analysis, with patients who did not die censored at 30 (or 90) days.

Step-by-step adjustment revealed that ethnicity had the greatest impact on explaining differences in postamputation mortality between these age-groups. Although the crude model showed that patients ≥75 years of age were at 34% greater risk of mortality within 30 days of a major amputation than those 50–64 years of age (and after adjustment for sex, had no impact [still 33%]), adjusting for ethnicity caused this disparity to increase to 62% (Table 4). The explanation is likely to be the difference in age structure between the Māori and European/other populations, whereby the Māori population has a younger age structure (29) as well as a higher risk of postamputation mortality. Little (if any) change was seen in the magnitude of this disparity when the other demographic, health system, and patient-level factors were added to the model.

Māori patients were at a greater risk of postoperative mortality than the European/other patients. In the fully adjusted model, Māori had a nearly 50% greater risk of dying within 30 days of a major amputation and a nearly 75% greater risk of dying after a minor amputation. This finding is consistent with other diabetes studies that observed differences in postamputation mortality outcomes among ethnic groups. For example, a U.S. study observed that African Americans had the highest mortality followed by non-Hispanic whites and Hispanics (20). Some evidence showed that Asian patients with diabetes (and, to a lesser degree, Pacific patients) are at increased risk of postamputation mortality compared with the European/other population; however, Asian and Pacific patients comprise a relatively small proportion of the total number of amputations, and thus, the confidence limits around respective estimates were wide and included the null.

Adjustment for age increased the disparity in postamputation mortality between

Table 3—Adjusted HRs for 30-day mortality by amputation type and further stratified by covariates

	Major amputation 30-day mortality adjusted HR (95% CI)[1]	Minor amputation 30-day mortality adjusted HR (95% CI)[1]
Sex		
Female	Reference	Reference
Male	0.87 (0.68–1.11)	1.02 (0.68–1.52)
Age (years)		
0–24	—[2]	—[2]
25–49	0.92 (0.58–1.48)	0.58 (0.22–1.54)
50–64	Reference	Reference
65–74	0.96 (0.68–1.34)	1.94 (1.09–3.46)
≥75	1.59 (1.15–2.18)	4.15 (2.45–7.03)
Ethnicity		
European/other	Reference	Reference
Māori	1.46 (1.08–1.98)	1.73 (1.02–2.94)
Pacific	1.11 (0.68–1.83)	1.74 (0.89–3.42)
Asian	1.75 (0.88–3.49)	1.49 (0.46–4.81)
Deprivation (NZDep)		
1–2	Reference	Reference
3–4	0.73 (0.42–1.28)	0.72 (0.26–1.98)
5–6	0.89 (0.54–1.48)	1.32 (0.58–3.04)
7–8	0.97 (0.6–1.56)	1.75 (0.81–3.81)
9–10	0.9 (0.56–1.46)	1.79 (0.81–3.92)
Rurality (URPC)		
Urban	Reference	Reference
Independent urban	0.88 (0.63–1.23)	1.2 (0.75–1.93)
Rural	1.24 (0.82–1.87)	1.54 (0.84–2.83)
Hospital volume (amputations/year)		
≥500	Reference	Reference
100–499	0.99 (0.77–1.29)	1.14 (0.75–1.72)
<100	0.86 (0.52–1.4)	0.78 (0.38–1.58)
Admission type		
Acute	1.44 (1.07–1.93)	1.43 (0.92–2.22)
Elective	Reference	Reference
Comorbidity (M3 index)[3]		
0	Reference	Reference
1	1.03 (0.78–1.35)	0.99 (0.64–1.52)
2	1.1 (0.78–1.55)	0.91 (0.54–1.55)
3	1.21 (0.85–1.73)	0.8 (0.45–1.43)

[1]Adjusted for all other covariates. [2]Insufficient data to calculate HRs. [3]HR at the given splined M3 index score value (e.g., score of 1 vs. score of 0).

Māori and European/other ethnic groups, but aside from a small reduction in disparity after the introduction of the admission type variable (likely as a result of postamputation mortality being more common among patients admitted acutely and Māori being more likely to be admitted in this way), the addition of other factors had little discernible impact on the disparity. Therefore, the difference in postamputation mortality risk among ethnic groups in New Zealand remains unexplained and requires further investigation.

No consistent evidence indicated that patient deprivation, rurality, or hospital volume are strongly associated with risk of postoperative mortality. Patients with an acute (as opposed to elective) admission were at an increased risk of postamputation mortality, an observation that is very much in keeping with trends reported across other surgical contexts (4,30).

Somewhat counterintuitively, the overall level of patient comorbidity (as measured with the M3 index) was not strongly associated with risk of postamputation mortality. By way of sensitivity analysis, we modeled the impact of the individual long-term conditions that comprise the M3 index on postoperative mortality, adjusting for all other covariates with the exception of the M3 index (data not shown). We observed no strong independent association between any of these conditions and the likelihood of death within 30 days of amputation. For example, risk of postoperative death after a major amputation was not increased for patients with peripheral vascular disease (adjusted HR 1.01 [95% CI 0.79–1.30]), chronic renal disease (0.98 [95% CI 0.77–1.25]), cerebrovascular disease (1.14 [95% CI 0.82–1.59]), congestive heart failure (1.05 [95% CI 0.80–1.38]), or previous myocardial infarction (1.15 [95% CI 0.86–1.53]).

Although surprising, our observations reflect those observed by Hoffstad et al. (11), who found that adjusting for both a comorbidity index (Charlson) and several individual comorbid conditions (including renal disease) did not change the magnitude of the association between lower-limb amputation and risk of death at any time among patients with diabetes. These observations could be explained by the fact that patients with uncontrolled risk factors may not qualify for amputation, meaning that those who undergo amputation are more likely to have stable comorbidity. As stated by Meara et al. (3), patients who are sickest and thus have the greatest risk of mortality may not undergo amputation for fear of killing the patient. However, nearly two-thirds of the current cohort had peripheral vascular disease, nearly one-half had renal disease, and more than one-quarter had congestive heart failure (Supplementary Material 2). Our cohort, therefore, was substantially ill; perhaps less so than those who might have been considered too unstable to undergo amputation, but unwell nonetheless. Amputation is a last resort, undertaken in an effort to preserve life. We do not know how long the patients in the current cohort would have lived had they not undergone amputation; however, we might at least assume that those who underwent a major amputation had a poor prognosis in the absence of treatment.

The primary strength of this study is that we used the entire prevalent cohort of patients with diabetes in New Zealand as the basis for our cohort definition and then included all amputations that occurred during our follow-up period. The use of a prevalent, well-defined cohort is a major strength because it improves the generalizability of the results to other contexts.

In terms of limitations, the study cohort was defined by using the VDR, a database that uses multiple variables

Table 4—Step-by-step adjusted HRs for 30-day mortality by amputation type for age (≥75 vs. 50–64 years) and ethnicity (Māori vs. European/other)

	Major amputation 30-day mortality adjusted HR (95% CI)[1]	Minor amputation 30-day mortality adjusted HR (95% CI)[1]
Age: ≥75 vs. 50–64 years (reference)		
Crude	1.34 (1–1.79)	3.02 (1.84–4.96)
Demographic factor		
Sex	1.33 (1–1.78)	3.01 (1.84–4.95)
Ethnicity	1.62 (1.18–2.22)	3.87 (2.29–6.55)
Deprivation	1.6 (1.16–2.19)	4 (2.36–6.77)
Rurality	1.6 (1.16–2.2)	4 (2.37–6.75)
Health system factor		
Hospital volume	1.59 (1.16–2.19)	4.04 (2.39–6.83)
Admission type	1.58 (1.14–2.17)	4.14 (2.45–7)
Patient-level factor		
Comorbidity	1.59 (1.15–2.18)	4.15 (2.45–7.03)
Ethnicity: Māori vs. European/other (reference)		
Crude	1.3 (1–1.68)	1.21 (0.75–1.94)
Demographic factor		
Age	1.58 (1.19–2.11)	2.06 (1.24–3.4)
Sex	1.55 (1.17–2.07)	2.06 (1.24–3.4)
Deprivation	1.56 (1.15–2.1)	1.82 (1.08–3.06)
Rurality	1.5 (1.11–2.04)	1.71 (1.01–2.9)
Health system factor		
Hospital volume	1.51 (1.11–2.04)	1.73 (1.02–2.93)
Admission type	1.46 (1.08–1.98)	1.72 (1.02–2.93)
Patient-level factors		
Comorbidity	1.46 (1.08–1.98)	1.73 (1.02–2.94)

[1]Adjusted for all other covariates.

from multiple national-level data sets to define diabetes status for individual New Zealanders. Like similar registers, the VDR is an imperfect measure of diabetes prevalence, although improvements have been made to the algorithm used to define the population over time (24). The hospitalization data used for this study included all publicly funded amputations undertaken in New Zealand (a country with universal health care), including publicly funded procedures performed at private facilities. It is possible that we missed amputations that were privately funded and then not reported to National Collections, but this likely would be a small proportion of amputations and unlikely to significantly affect the findings. Although this article describes postamputation mortality among the cohort as well as how this mortality differs according to demographic-, system-, and patient-level factors, it does not provide details regarding the mechanisms by which these deaths occur; in other words, this article describes the what but not the why. Additional detailed investigation is required to understand the role of factors such as frailty, infection (including preoperative sepsis [14,31]), reduced capability for healing, and markers of postoperative quality of care. Data for these factors were not available in the routine data sources we used.

In conclusion, we observed in a national prevalent cohort of patients with diabetes a high rate of mortality among those who underwent amputation: >11% of patients who underwent a major amputation died within 30 days, whereas nearly 18% died within 90 days. Death was most common among older patients, with those ≥75 years of age at a 59% greater risk of dying within 30 days of a major amputation and at a four times greater risk of dying within 30 days of a minor amputation (adjusted for sex, ethnicity, deprivation, rurality, hospital volume, admission type, and patient comorbidity). Indigenous Māori were at a 46% greater risk of dying within 30 days of a major amputation and a 73% greater risk of dying within 30 days of a minor amputation. These disparities are unexplained and require further investigation. Sex, deprivation, rurality, hospital volume, and comorbidity were not consistently independently associated with risk of postoperative mortality. More work is required to investigate the mechanisms of postoperative mortality among patients with diabetes who undergo amputation.

Acknowledgments. The authors thank Ilya Ratine and Simon Ross from the New Zealand Ministry of Health for their assistance with the data extraction. Data linking and extraction were performed by the National Collections staff at the New Zealand Ministry of Health.

Funding. This study was partially funded by a University of Otago, Wellington Dean's Grant.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. J.K.G. led the study concept and design and analysis and interpretation of data, drafted the manuscript, and revised the content on the basis of feedback. J.S. assisted with the study concept and design and interpretation of data and provided critical revision of drafts. J.R.-S. assisted with the study design and interpretation of data and provided critical revision of drafts. S.Y. assisted with interpretation of data and provided critical revision of drafts. D.S. assisted with study concept and design, assisted with interpretation of data, and provided critical revision of drafts. J.K.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. World Health Organization. *WHO Guidelines for Safe Surgery 2009: Safe Surgery Saves Lives*. Geneva, Switzerland, World Health Organization, 2009
2. Yu P, Chang DC, Osen HB, Talamini MA. NSQIP reveals significant incidence of death following discharge. J Surg Res 2011;170:e217–e224
3. Meara JG, Leather AJ, Hagander L, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. Lancet 2015;386:569–624
4. Perioperative Mortality Review Committee. *Perioperative Mortality in New Zealand: Fifth Report of the Perioperative Mortality Review Committee*. Wellington, New Zealand, Health Quality & Safety Commission, 2016
5. Watters DA, Hollands MJ, Gruen RL, et al. Perioperative mortality rate (POMR): a global indicator of access to safe surgery and anaesthesia. World J Surg 2015;39:856–864
6. Johannesson A, Larsson GU, Ramstrand N, Turkiewicz A, Wiréhn AB, Atroshi I. Incidence of lower-limb amputation in the diabetic and nondiabetic general population: a 10-year population-based cohort study of initial unilateral and contralateral amputations and reamputations. Diabetes Care 2009;32:275–280
7. Trautner C, Haastert B, Giani G, Berger M. Incidence of lower limb amputations and diabetes. Diabetes Care 1996;19:1006–1009
8. Trautner C, Haastert B, Giani G, Berger M. Amputations and diabetes: a case-control study. Diabet Med 2002;19:35–40
9. Fosse S, Hartemann-Heurtier A, Jacqueminet S, Ha Van G, Grimaldi A, Fagot-Campagna A. Incidence and characteristics of lower limb amputations in people with diabetes. Diabet Med 2009;26:391–396
10. Tentolouris N, Al-Sabbagh S, Walker MG, Boulton AJ, Jude EB. Mortality in diabetic and

nondiabetic patients after amputations performed from 1990 to 1995: a 5-year follow-up study. Diabetes Care 2004;27:1598–1604
11. Hoffstad O, Mitra N, Walsh J, Margolis DJ. Diabetes, lower-extremity amputation, and death. Diabetes Care 2015;38:1852–1857
12. Schofield CJ, Libby G, Brennan GM, MacAlpine RR, Morris AD, Leese GP; DARTS/MEMO Collaboration. Mortality and hospitalization in patients after amputation: a comparison between patients with and without diabetes. Diabetes Care 2006;29:2252–2256
13. Icks A, Scheer M, Morbach S, et al. Time-dependent impact of diabetes on mortality in patients after major lower extremity amputation: survival in a population-based 5-year cohort in Germany. Diabetes Care 2011;34:1350–1354
14. Hambleton IR, Jonnalagadda R, Davis CR, Fraser HS, Chaturvedi N, Hennis AJ. All-cause mortality after diabetes-related amputation in Barbados: a prospective case-control study. Diabetes Care 2009;32:306–307
15. Papazafiropoulou A, Tentolouris N, Soldatos RP, et al. Mortality in diabetic and nondiabetic patients after amputations performed from 1996 to 2005 in a tertiary hospital population: a 3-year follow-up study. J Diabetes Complications 2009;23:7–11
16. Thorud JC, Plemmons B, Buckley CJ, Shibuya N, Jupiter DC. Mortality after nontraumatic major amputation among patients with diabetes and peripheral vascular disease: a systematic review. J Foot Ankle Surg 2016;55:591–599
17. Subramaniam B, Pomposelli F, Talmor D, Park KW. Perioperative and long-term morbidity and mortality after above-knee and below-knee amputations in diabetics and nondiabetics. Anesth Analg 2005;100:1241–1247
18. Yamada K, Yasunaga H, Kadono Y, et al. Postoperative outcomes of major lower extremity amputations in patients with diabetes and peripheral artery disease: analysis using the Diagnosis Procedure Combination database in Japan. Am J Surg 2016;212:446–450
19. Aragón-Sánchez J, Hernández-Herrero MJ, Lázaro-Martínez JL, et al. In-hospital complications and mortality following major lower extremity amputations in a series of predominantly diabetic patients. Int J Low Extrem Wounds 2010;9:16–23
20. Lavery LA, van Houtum WH, Armstrong DG, Harkless LB, Ashry HR, Walker SC. Mortality following lower extremity amputation in minorities with diabetes mellitus. Diabetes Res Clin Pract 1997;37:41–47
21. Ang Y, Yap CW, Saxena N, Lin LK, Heng BH. Diabetes-related lower extremity amputations in Singapore. Proc Singapore Healthc 2017;26:76–80
22. Ministry of Health. Virtual Diabetes Register (VDR) [article online], 26 May 2017. Available from http://www.health.govt.nz/our-work/diseases-and-conditions/diabetes/about-diabetes/virtual-diabetes-register-vdr. Accessed 26 June 2017
23. Jeffcoate WJ, van Houtum WH. Amputation as a marker of the quality of foot care in diabetes. Diabetologia 2004;47:2051–2058
24. Health Information Standards Organisation. *HISO 10001:2017 Ethnicity Data Protocols*. Wellington, New Zealand, Ministry of Health, September 2017
25. Salmond CE, Crampton P. Development of New Zealand's deprivation index (NZDep) and its uptake as a national policy tool. Can J Public Health 2012;103(Suppl. 2):S7–S11
26. Statistics New Zealand. *New Zealand: An Urban/Rural Profile Update*. Wellington, New Zealand, Statistics New Zealand, 2008
27. Stanley J, Safarti D. Development and validation of the M3 index for measuring multimorbidity load for risk of mortality. J Clin Epidemiol 2017;95:99–110
28. Harrell FE Jr. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. Cham, Switzerland, Springer, 2015
29. Ministry of Health. Age structure [article online], 2015. Available from https://www.health.govt.nz/our-work/populations/maori-health/tatau-kahukura-maori-health-statistics/tatauranga-taupori-demographics/age-structure. Accessed 12 January 2017
30. Perioperative Mortality Review Committee. *Perioperative Mortality in New Zealand: Sixth Report of the Perioperative Mortality Review Committee*. Wellington, New Zealand, Health Quality & Safety Commission, 2017
31. O'Brien PJ, Cox MW, Shortell CK, Scarborough JE. Risk factors for early failure of surgical amputations: an analysis of 8,878 isolated lower extremity amputation procedures. J Am Coll Surg 2013;216:836–842; discussion 842–844