The Journal of Foot & Ankle Surgery 55 (2016) 591–599

Contents lists available at ScienceDirect

The Journal of Foot & Ankle Surgery

journal homepage: www.jfas.org

Mortality After Nontraumatic Major Amputation Among Patients With Diabetes and Peripheral Vascular Disease: A Systematic Review

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A R T I C L E I N F O

Level of Clinical Evidence: 2

Keywords:
above-the-knee amputation
below-the-knee amputation
death
renal disease
survival

A B S T R A C T

High mortality rates have been reported after major amputations of a lower limb secondary to diabetes and peripheral vascular disease. However, the mortality rates have varied across studies. A systematic review of the 5-year mortality after nontraumatic major amputations of the lower extremity was conducted. A data search was performed of Medline using OVID, CINHAL, and Cochrane, 365 abstracts were screened, and 79 full text articles were assessed for eligibility. After review, 31 studies met the inclusion and exclusion criteria. Overall, the 5-year mortality rate was very high among patients with any amputation (major and minor combined), ranging from 53% to 100%, and in patients with major amputations, ranging from 52% to 80%. Mortality after below-the-knee amputation ranged from 40% to 82% and after above-the-knee amputation from 40% to 90%. The risk factors for increased mortality included age, renal disease, proximal amputation, and peripheral vascular disease. Although our previous systematic review of the 5-year mortality after ulceration had much lower rates of death, additional studies are warranted to determine whether amputation hastens death or is a marker for underlying disease severity.

The Centers for Disease Control has estimated that in 2014, 29.1 million adults in the United States, or 9.3% of the adult population, had diabetes (1). Of those aged ≥65 years, the Centers for Disease Control has estimated that 11.2 million (25.9%) have diabetes. An estimated 5% to 7% of patients with diabetes will develop diabetic foot ulceration (2,3). This ulceration can precipitate amputation and, ultimately, in concert with diabetes-associated peripheral vascular disease (PVD), can lead to death (4,5). Lower extremity amputation is roughly 10 times as likely in those with diabetes as in those without diabetes (6,7), and this risk might increase further in those with diabetic foot ulceration (8,9).

Lower extremity amputation secondary to diabetic foot ulceration can have a devastating effect on overall patient health and psychology (10–13) and is thought to lead to excessive premature death (14–20) and to have negative effects on vascular dynamics (21–23). Limb salvage is thus of interest because it could preserve quality of life (24) and minimize the risk of deconditioning (25). However, a recent systematic review has questioned whether patients' quality of life changes with amputation (26). Furthermore, it is uncertain whether amputation hastens death or whether the patient's underlying condition is already worse for those requiring amputations. In an earlier systematic review, we attempted to determine the approximate 5-year mortality after the onset of diabetic foot ulceration and found this to be roughly 40% (27). That review also highlighted the difficulties in identifying the causal relationships among ulceration, amputation, and death.

To add complexity to this issue, above and beyond the indications for amputation, a surgeon and/or patient might make a conscious decision in terms of the timing or type of amputation. Amputation

Financial Disclosure: None reported.
Conflicts of Interest: None reported.

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http://dx.doi.org/10.1053/j.jfas.2016.01.012

rates have been shown to vary by geographic location (28). Some physicians will even use a limited life expectancy as part of the indication for a major amputation (29). These differences in practice patterns make the interpretation of a single study difficult, because the culture of decision-making for amputation could be dependent on the geographic areas, dates of the study, and individuals' personal viewpoints. To gain a more general understanding of mortality after major amputation secondary to diabetic complications, the present study reviewed all studies that reported the 5-year mortality after major amputation in patients with nontraumatic amputations, with a focus on diabetes as a subset of the analysis. Although this cannot necessarily answer the question of whether amputation hastens death, it should aid in the understanding of mortality after major amputations.

Materials and Methods

On April 23, 2014, 4 of us (J.C.T., N.S., D.C.J., B.P.) participated in the following systematic search for reports relating to the rates of death after major amputation. We searched Medline using OVID, CINAHL, and the Cochran Central database with the following search terms: ("amput*") and ("foot" or "feet" or "lower extremit*") and ("PVD" or "peripheral vascular disease" or "diabet*"), and ("death" or "survival" or "mortality").

We aimed to keep our review as broad as possible, excluding lower quality studies. We searched for reports published from January 1, 1980 to April 23, 2014 and required that abstracts were available. No language restrictions were placed on the searches. Searching in OVID was limited to core clinical journals and human-related results.

To filter the abstracts and then the full studies, we used the following criteria. We included only human studies, allowing cohort studies, longitudinal studies, case-control studies, cross-sectional studies, and prospective clinical trials. We excluded case series, letters, systematic reviews or meta-analyses (although these were all searched for the purpose of obtaining additional references), and abstracts or studies that included only traumatic amputation. We required that the follow-up period after the initial presentation was a mean of $\geq$5 years or that the Kaplan-Meier estimates for 5-year survival were presented. We allowed studies examining primary major amputations, including below-the-knee (BKA), above-the-knee (AKA), and hip disarticulation. We allowed studies that had included both major and minor (distal to BKA) amputations; however, the studies that reported only minor amputations were excluded.

Each report was summarized by 1 of 3 of us (J.C.T., D.C.J., B.P.). These reports were then reviewed by 4 of us (J.C.T., D.C.J., N.S., B.P.) for accuracy and organized into one of the groups of studies shown in the Results section (major and minor reported together, major and minor reported separately, and major only; Tables 1 to 3). The final data were reviewed and approved by all of us. The summaries included the study year and location, number of patients in the study, distribution of the patients into the study groups, mean age within the study groups, distribution of gender within the study groups, distribution of diabetes within the study groups, mortality rate within the study groups, mean follow-up times or time at which survival was estimated with Kaplan-Meier estimates, the reason for amputations within the study groups, study setting, and the risk factors identified as associated with mortality, either in the entire study population or within specific study groups. Each study included was examined for its reporting of age, diabetes, and renal concerns and whether these were associated with mortality. The main outcome measure was 5-year mortality for patients who had undergone major amputations. Estimates were determined from all included studies in which the 5-year mortality estimates were available. The estimates were compiled separately for the major amputations reported (combined BKA and AKA, BKA only, and AKA only). The issues of outcome level bias were discussed at the beginning of our report, and study bias was assessed using the Newcastle-Ottawa scale (30).

Because we observed some patterns in the association between age and mortality, we performed an initial evaluation of the relationship between the mean age of the patients in the studies and the 5-year mortality. The details of the evaluation are provided in full detail in the Supplemental Methods section and Supplemental Table S4.

Results

A total of 340 abstracts were identified through the database searches (Fig. 1). We recovered 118 abstracts from Cochrane, 89 abstracts from OVID, and 133 abstracts from CINAHL. We selected 45 full text reports for review after examining these abstracts. Additionally, 44 studies were identified for full text review from reviewing the references of the 45 previous full text reports. Nine duplicates were identified, and after removal and screening of the 384 abstracts, 89 full text articles were assessed for eligibility. After review, 31 studies met our inclusion and exclusion criteria (Fig. 2). Two reports (Inderbitzi et al [31,32] in 1992 and 2003) were identified as having the same cohort of patients and were combined and used as 1 source in the present review.

Although all included studies were required to report on major amputations, the method of reporting the mortality rates differed and could be separated into 1 of 3 categories: mortality with major and minor amputations combined (Table 1), mortality with major and minor amputations reported separately (Table 2), and mortality reported only for major amputations (Table 3).

Table 1
Major and minor amputations combined

Investigator	Patients (n)	Mean Age (y)	Male Gender (%)	Diabetes (%)	5-y Mortality (%)
Lavery et al, 2010 (56)	1043 (minor 45.7%, BKA 32.3%, AKA 22%)	64.82 ± 12.4 (range 27 to 97)	59.1	100	53
Heikkinen et al, 2007 (33)	1371		53.5		
Male	42% AKA, 32% BKA, 27% minor	67.9 ± 15.5		35	Male data only: 91%, DM; 74%, non-DM
Female	49% AKA, 29% BKA, 22% minor	75.2 ± 13.9		38	
Tseng et al, 2008 (54)	358 (278 major and 85 minor)	66.6 ± 10.3	53.4	100	59.8
Schofield et al, 2006 (35)	390				
DM	119 (66 major, 53 minor)	69.9 ± 11.8	62.2	100	68
Non-DM	271 (159 major, 112 minor)	70.6 ± 15.8	43.9	0	57.2
Tentolouris et al, 2004 (34)	251 minor and major				
DM	100 (46 major, 54 minor)	64.2 ± 11	62	100	56
Non-DM	151 (65 major, 86 minor)	67.8 ± 10	72.8	0	56
Resnick et al, 2004 (20)	134 (80 minor, 53 BKA, 1 AKA)	58.1	52	100	76*
Larsson et al, 1998 (9)	189 minor and major		57	100	68
Minor	93	65 (range 32 to 94)			
Major	96	74 (range 42 to 91)			
Inderbitzi et al, 1992 and 2003 (31,32)	66 (initial amputations, minor 19, BKA 88, AKA 25), bilateral amputations	63.1, first amputation; 67.7, second amputation (range 34-91)	69.7	61	69
Jamieson et al, 1983 (36)	56 (73 legs total; 2 TMA, 23 BKA, 38 AKA or knee disarticulation)	NR (85.7% aged >60 y)	53.6	13	100

Abbreviations: AKA, above-the-knee amputation; BKA, below-the-knee amputation; DM, diabetes mellitus; NR, not recorded; SD, standard deviation; TMA, transmetatarsal amputation.
Data presented as mean ± SD, unless otherwise noted.
* Data were not taken from estimated 5-year mortality.