Early post-operative mortality after major lower limb amputation: a systematic review of population and regional based studies

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What does this review add to the existing literature and how will it influence future clinical practice?

The population undergoing major lower limb amputation have a notorious association with mortality. Based on a systematic review of the literature, we show that 30-day and in-hospital mortality rates vary between 4 and 22% in population and regional-based studies. With the aim of providing direction for improvements in both clinical care and research, we demonstrate the need for detailed information to enable appropriate investigation of the relationship between population characteristics and post-operative mortality to better explain this variation. While it is currently unclear what these factors may be, it is clear that agreement through a coordinated process will improve current knowledge.

Abstract

Objectives: Lower limb amputation is a procedure frequently associated with a high risk of early post-operative mortality. Mortality rates are also increasingly being put forward as a possible benchmark for surgical performance. The primary aim of this systematic review is to investigate early post-operative mortality following a major lower limb amputation in population/regional-based studies, and reported factors that might influence these mortality outcomes.

Design: Systematic review

Methods: Embase, PubMed, Cinahl and Psycinfo were searched for publications in any language on 30-day or in-hospital mortality after major lower limb amputation in population/regional-based studies. PRISMA-guidelines were followed. A self-developed checklist was used to assess quality and susceptibility to bias. We extracted summary data for percentage of population who died; pooling of quantitative results was not possible due to methodological differences between studies.

Results: Of the 9082 publications identified, results from 21 were included. The percentage of the population undergoing amputation who died within 30-days ranged from 7-22%, the in-hospital equivalent was 4-20%. Transfemoral amputation and older age were found to have a higher proportion of early post-operative mortality, compared to transtibial and younger age respectively. Other patient factors or surgical treatment choices related with increased early post-operative mortality varied between studies.

Conclusions: Early post-operative mortality rates vary from 4 to 22%. There is very limited data presented for patient-related factors (age, comorbidities) that influence mortality. Even less is known on factors related to surgical treatment choices, being limited to amputation level. More information is needed to enable any comparison across studies or for any benchmarking of acceptable mortality rates. Agreement on key factors to be reported needs to be agreed.

Keywords: operative surgical procedure; postoperative complications; benchmarking; amputation; mortality; systematic review;

Introduction

Major lower limb amputation is a procedure frequently associated as having a high risk of post-operative mortality.[1-4] This is generally attributed to the relative older age and the high prevalence of cardiovascular comorbidities in the population undergoing the procedure, the amputation being a sign of end-stage disease and multi-organ failure; but it has also been labelled as a failure of care.[5] Increasingly, data driven benchmarks for outcomes are requested by national bodies who seek to ensure standardised care for patients.[6] However, it is not clear for the population with amputation what might be considered an acceptable outcome, including that of acceptable early post-operative mortality rates.

A range of factors are thought to be related to post-operative mortality after amputation, including comorbidities (e.g. diabetes mellitus, cardiac disease or renal insufficiency), the setting in which the procedure takes place and a person's status at the time of surgery. These factors may provide additional information about who is most at risk of dying within the population undergoing amputation. Highest early post-operative mortality percentages are seen in clinical practice for older patients and those undergoing amputation at the transfemoral level, but it is unknown if this difference is found consistently in population-based studies, as an overview of early post-operative mortality after major lower limb amputation based on a systematic review of the literature is not available.

The risk of early post-operative mortality is an important consideration on which patients and surgeons base their decision firstly to undergo the procedure, and secondly the subsequent details such as level of the surgery. However, there is currently little consistency in the way data are presented. Summarising the published literature will aim to provide a minimal standard to which National registries, such as the UK vascular registry, can work to include relevant information. This information might also provide useful benchmarks for comparing prognostic outcomes to gain a deeper understanding of factors contributing to mortality.

The primary aim of this systematic review is to investigate early post-operative mortality following a major lower limb amputation in population or regional-based studies. Secondary aims are to evaluate what is known about the relationship between early post-operative mortality and reported factors that might influence these mortality outcomes.

Materials and Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[7] and was prospectively registered at PROSPERO (CRD42012002241).

Search strategy

Because death is a frequent outcome within amputation populations, mortality is often included as a secondary outcome alongside a primary aim, for example, when a rehabilitation outcome is presented and a percentage of the population will have died in the time of follow up. In an effort to not immediately exclude such studies, the search strategy was purposefully designed to be broad and inclusive, using the terms: "Mortality OR Death OR Survival" AND "Amput*" and searching in all fields.

Four databases were searched (Embase via OvidSP, PubMed, Cinahl, Psycinfo) including publications dated from 1 January 2000 to 30 July 2015, published in any language. The original search took place on 1 May 2012, and was updated on 30 July 2015 (see Figure 1). Publications that focused exclusively on amputations distal to the ankle joint (i.e. 'minor amputations' [8]), or other parts of body were excluded. Minor amputations were excluded as these are generally performed in a population with different mortality from those undergoing major amputation (e.g. [9-11]).

Study selection

Two investigators (JVN and JH) independently screened all titles and abstracts for relevance to mortality or survival in a population with major lower limb amputation, from any cause. If either investigator scored the publication positively in the title phase, it was included to the next stage. Inclusion was based on: 1. Any incidence or population data (with an indication of a potential link to mortality); 2. Amputation is the primary outcome of a retrospective cohort study where the term 'mortality' (or a synonym of) is mentioned; 3. Amputation versus other 'treatment' (e.g. limb salvage) where the term 'mortality' (or a synonym of) is mentioned. Abstracts were excluded if: 1. Amputation versus other 'treatment' (e.g. limb salvage) where the term 'mortality' (or a synonym of) is not mentioned; 2. The primary outcome is NOT amputation (e.g. primary outcome is other surgical procedure) and there is no immediate reference to amputation and mortality. In the abstract phase, differences on decisions for inclusion were discussed between the two investigators.

Full text publications were independently screened by two investigators (LVF and JVN). Early post-operative mortality was defined as either 30-day mortality (i.e. death within 30 days after the amputation operation date) or in-hospital mortality (i.e. death within the period of hospitalization immediately following the operation). Articles were included if early post-operative mortality was a primary outcome of the study. Only publications reporting data from population-based studies were included. Population-based was defined as any study across broad (regional or national) and well-defined populations, with numbers or percentages of key characteristics within this population presented. Data from single or selected centres was not considered reflective of the general population and therefore excluded. Foreign language articles were evaluated by a native speaker who had experience in an academic or medical setting. None were included in the final set of publications.

Quality and susceptibility to bias

Since no specific quality assessment instrument was suited to our data and research aim, a self-developed approach had to be followed. In line with conclusions from a systematic review on tools for assessing the quality and susceptibility to bias in observational studies,[12] a transparent checklist approach was chosen, concentrating on the few, principal, potential sources of bias. Our self-developed checklist was broadly based on the MOOSE guidelines[13] and the Newcastle-Ottawa scale,[14] and aimed to assess selection and information bias. Four criteria were assessed by two investigators (LVF and JVN) independently (Table 1). Each criterion was scored with a '+', '?', or '-'. Disagreements were solved by discussion until consensus was reached. The criteria chosen were based primarily on the completeness of the population included, known to be an important aspect of bias in amputation research,[15] and included the method of identifying information and the description of the population. Specific attention was given to reporting of amputation level as this is likely to impact on risk of mortality.

Data extraction

Data from each study was extracted by one investigator (JVN or LVF), after which the other investigator checked the extracted data. Data extracted concerned setting, country, period, number of patients, included levels of amputation, included population, percentage of the population with diabetes mellitus, amputations being the first-ever or any, age and gender of the population, 30-day or in-hospital mortality of all included patients and of specific subgroups per age, level, diabetes or no diabetes, and subgroups reported in multivariate analyses, including statistical values if subgroups were compared. Authors were contacted if data to be extracted was unclear from the original publication.

Results

Of 9082 publications identified in the original and updated search, 22 publications met all inclusion criteria (Figure 1). Two publications reported findings from the same population using similar multivariate analyses;[16,17] the publication that reported the most population details was included in the results.[16] Presentation of data from 21 studies included contains eleven publications reporting 30-day mortality, eight publications reporting in-hospital mortality, and two publications reporting both (Figure 1)[1-4,9-11,16,18-30]. Data and findings could not be pooled as the studies had differing inclusion and provided varied outcomes (i.e. no quantitative analyses were performed; Figure 1). Presented below are the major overarching findings of the included papers, with details of the original authors' analyses presented in the tables.

Data in included studies were collected through hospital records directly or through national surgical registries. Thirteen out of twenty-one publications presented data from United States (US) databases, with six publications presenting data obtained from the same database (American College of Surgeons National Surgical Quality Improvement Program [ACS NSQIP]) in the same time period. Three publications presented data from English Hospital Episode Statistics (HES) in the same time period. From the information presented on the populations included in these studies, potential overlap between studies reporting results of the same database could not be reliably determined, and as such descriptive data of all studies are given. To avoid analysing these data multiple times, results from these studies on the relation between mortality and patient factors will be reported separated from the other studies, as either "ACS NSQIP database" or "HES database".

30-day mortality

The susceptibility to bias of the thirteen included publications that reported 30-day mortality varied, with five publications meeting all four criteria, and three publications meeting only one (Table 2). The number of included patients ranged from 299 to 186338. In terms of population studied, most publications included both transtibial and transfemoral amputations, exclusion criteria varied (e.g. none, terminal patients only, amputations as a result of cancer and trauma), population with diabetes ranged from 39 to 69%, inclusion of first amputation only or any amputation varied, and the population was generally older with a mean age >65 years (Table 2).

30-day mortality ranged from 7 to 22% for all included patients (Table 3). 30-day mortality was lower after transtibial compared to transfemoral amputations, with differences ranging from 4-9% within studies (Table 3). This was found to be a statistically significant difference in the ACS NSQIP database and in the two other studies where this was tested (Table 3). No differences between 30-day mortality in patients with and without diabetes were found in the ACS NSQIP database and two other studies (1-4% difference within studies, Table 3); a statistically significant lower 30-day mortality for patients with diabetes was found in one study (9% difference, $p<0.05$; Table 3).

Variables related with 30-day mortality in multivariate analyses are shown in Supplementary Table 1. Age at time of amputation was considered in the ACS NSQIP database and in two other studies. Older age was associated with higher mortality risk; the only exception was patients undergoing below-knee amputation in one study, although patients who died were significantly older in univariate analyses. Of the comorbidities investigated, patients with end-stage renal disease were found to have a higher mortality risk in the ACS NSQIP database and in patients undergoing below-knee amputation in one study; no significantly higher early post-operative mortality was found for patients with end-stage renal disease undergoing above-knee amputation in another study. Cerebrovascular disease was significantly associated with higher mortality in the two studies that did investigate this; this was not investigated from the ACS NSQIP database. Concerning the patients' status at the time of surgery, those who were totally dependent or with do not resuscitate order presented with higher 30-day mortality, as did those with pre-operative sepsis in the ACS NSQIP database.

In-hospital mortality

The susceptibility to bias of the ten included publications varied, with two publications meeting all four criteria, five publications meeting three out of four, and three meeting one or two out of four (Table 4). The number of included patients ranged from 2375 to 64710. In terms of population, all publications included both transtibial and transfemoral amputations, exclusion criteria varied (e.g. none, terminal patients only, amputations as a result of cancer and trauma), population with diabetes ranged from 39 to 89%, eight publications included any amputation, and the population was generally older with a mean age >65 years (Table 4). Mean or median length of stay ranged from 9 to 50 days, with high standard deviations (28-52), but length of stay was frequently not reported.

In-hospital mortality ranged from 4-20% for all included patients (Table 5). In-hospital mortality was lower after transtibial compared to transfemoral amputations, with differences within studies ranging from 5-10% (Table 5); this was a statistically significant difference in the HES database and the three other publications where this was tested (Table 5). The difference between patients with or without diabetes was investigated in the HES database and one other study. Whereas a reduced in-hospital mortality risk for patients with diabetes was found in the HES database (Odd's Ratio 0.55 for men and 0.58 for women; Table 5), this difference was not significant in the other study.

Variables related with in-hospital mortality in multivariate analyses are shown in Supplementary Table 2. In the ACS NSQIP and HES databases and in two studies, older age was associated with higher mortality risk; the effect of age was not significant in one other study. Of the comorbidities investigated, patients with end-stage renal disease (ACS NSQIP and HES databases and one study) and patients with a higher score on the Charlson Comorbidity Index or higher illness severity (HES database and one study) were found to have a higher in-hospital mortality risk; this was found for patients with type 2 DM only in another study. Concerning the patients' status at the time of surgery, those with systemic inflammatory response presented with higher in-hospital mortality in the ACS NSQIP database and two studies; this was not investigated in the HES database.

Discussion

Early post-operative mortality rates vary from 4 to 22% between studies. [1-4,9-11,16,18-30] In order to explain some of this variation, patient factors and surgical treatment options explored in the studies were extracted. These factors were not consistently or adequately reported in the studies, limiting our ability to fully investigate their influence on early post-operative mortality. Agreement across settings on key factors to be reported in future studies is recommended. A coordinated process, similar to that which other conditions have benefited from through initiatives like the Core Outcome Measures in Effectiveness Trials (COMET; http://www.comet-initiative.org) or the Outcome Measures in Rheumatology (OMERACT; http://www.omeract.org/), will increase current knowledge. At a minimum, reportable population factors that might be discussed in such a forum include: level of amputation, whether it was the first-ever or a subsequent amputation, the reason for amputation, the patient's age and sex, and whether the amputation was performed as an emergency or planned procedure. Additionally, the distribution of age, sex and size of the general population, the geographical region and information on participating centres might be considered relevant for population-based studies, to better compare the different populations. However, until such information is further explored, no definitive factors can be suggested. Agreement on factors to be included, and subsequent consistent reporting of these, is needed before early post-operative mortality rates can be considered for use as benchmark across settings.

Influential patient factors (age, comorbidities) on mortality were inconsistent between studies. Age, end-stage renal disease, cerebrovascular disease, systemic inflammatory response at the time of operation, and being totally dependent on assistance for activities of daily living, were found as important factors in most, but not all, studies. As almost no study provided sufficient detail on early post-operative mortality for different subgroups, results of the studies could not be pooled or accurately compared for more detailed analysis of these findings. One major reason for this is that studies use different inclusion criteria. As an example, eighteen studies did not separate information for people undergoing their first major amputation and those having a subsequent major amputation. [2,4,9-11,16,18-21,23-30] This limits a fair comparison between two groups of patients that are different for surgeons when seen in clinical practice; people undergoing their first major amputation are likely to be in better condition than those undergoing subsequent amputation on the ipsilateral or contralateral limb. As the variables investigated for their influence on mortality were so varied, with only a few studies looking at the same patient factors or treatment parameters, we have presented qualitative and descriptive data from the studies in supplementary tables with the view that this information will demonstrate the need for improvements in reporting and gaps in current knowledge. The differences in early post-operative mortality found in the studies are discussed below with consideration to patient factors, surgical choices and treatment pathways.

Within the population of patients undergoing an amputation, higher early post-operative mortality rates were found for those with a higher age.[2-4,20,21,24,25,30] Within a population that is already old (mean age >65), the oldest patients had a higher mortality risk. Further, various underlying diseases are found in the population undergoing amputation. Diabetes is a key factor of interest, which was reported to be present in 39-89% of the population in the included studies. The difference in the percentage of people with diabetes may be explained by inclusion criteria (e.g. the percentage of people with diabetes is known to be higher in transtibial amputations, and some studies included only transtibial amputations [21]), as well as differences between countries and study settings. Findings on early post-operative mortality in relation to diabetes were mixed and inconclusive: no influence from diabetes on early post-operative mortality was found in the ACS NSQIP database and three studies,[3,4,11,18,25] whereas in the HES database and one study lower early post-operative mortality percentages were found for people with diabetes.[1,2] Findings on other patient factors varied greatly between studies and there was wide variation in the parameters investigated. End-stage renal disease, cerebrovascular disease, systemic inflammatory response at the time of operation, and being totally dependent on assistance for activities of daily living were the most frequently reported factors of interest.

While population characteristics are present and unable to be modified by the time people are requiring amputation, there are choices around surgery and the treatment pathway that might also influence mortality. The most obvious of these is often considered to be the amputation level, with early post-operative mortality rates being lower after transtibial compared to transfemoral amputations.[2,3,9,10,18,20,23,24,26,28-30] However, amputation at a lower level is also generally indicative of a less significant disease or infection process rather than simply a surgical choice. Not surprisingly, this additional level of health may provide protection from both a more proximal amputation and earlier mortality. Other factors around surgery and treatment pathway may also impact outcomes, including the timing of the operation, resources attributed in the pre-operative period to the person facing amputation, and the skills and experience of the surgical team. Timing of amputation has been linked to mortality, with risk of in-hospital death increasing by 2% for each day waited, and well-planned elective amputations resulting in lower mortality risks than emergency amputations.[2] Another study found an association between the involvement of a surgical resident (i.e. during the surgical training period) and a higher percentage of adverse outcomes, although this might also be explained by their greater involvement in emergency operations.[16,17] In the ideal setting, major amputations should be carefully planned and performed by an experienced surgical team, and consideration of these factors should be included in research outcomes.

Looking further at the preoperative treatment pathway and the timing of amputation, recent perspectives have developed around being more aggressive with amputation, by operating sooner, choosing a more proximal level initially, or making a choice not to amputate at all. Continued attempts at limb salvage, through (endo-)vascular procedures, medications or prolonged hospitalisation and immobility may be disadvantageous to some patients.[31] This perspective has been termed 'choosing life or limb',[32] and provides reasoning that a person at risk needs to make an informed decision, ideally before their limb has reached a critical stage. Any change toward a more aggressive approach might lower early post-operative mortality, as people will be operated earlier in their life at a moment when concurrent cardiovascular disease might still be in an earlier stage. Such early intervention is not a new idea, having been used for the population with trauma who are considering limb salvage versus amputation,[33] and for younger people with diabetes.[34] For the older population with vascular disease, early amputation might reduce the lengthy periods of immobility and hospitalisation when attempts to heal the limb are pursued.[31] It is during this time that a substantial decrease in physical condition and function can occur, leading to higher risk of mortality or, for those who survive, a reduced quality of life and poorer potential for good rehabilitation outcomes after an amputation.[35,36,37] However, data underpinning these types of decisions was not available from any of the included studies. The preoperative treatment pathway and timing of amputation should be further investigated and discussed to better understand its influence on amputation outcomes.

For this systematic review we excluded a large number of studies that were not considered population/regional-based. While informative, these single centre studies are much more likely to be impacted by selection bias (particular in light of growing evidence of hospital/surgical influence on mortality outcomes). A limitation with this review is that sixteen of the twenty-one included studies were from the US or the UK, with the majority of the US studies coming from the same database (ACS NSQIP) and the same period (2005-2010). Another limitation is owing to healthcare databases and the availability of only selected information. For example, in ACS NSQIP functional status is only given in three levels, although more information on frailty and mobility limitations would be useful in this population. However, the basic information in these databases, and additional advantages of large population data, suffices when adequately reported information is included.

In conclusion, early post-operative mortality rates in population/regional-based studies were found to vary from 4 to 22%. While there was some data presented for patient factors (age, comorbidities) that influence mortality, this was not consistent between studies. Even less is known on surgical treatment choices, being limited to the choice of amputation level. It is difficult to know what is really required with regard to minimally important factors or standard reporting. While we can make suggestions from clinical inferences of level of amputation, whether it was the first-ever or a subsequent amputation, the patient's age and sex – we have no evidence if these are indeed what is required or what other factors might be required. Only with agreement on these key factors, and their consistent reporting, can we start to fully investigate the influences on early post-operative mortality and subsequently, possibilities to lower this risk with surgical choices and changes in the treatment pathway.

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Table 1: Overview of the system for quality and susceptibility to bias assessment of included studies

A – Quality of description of included area or data sources	
+	Clear description of geographic region and participating centres in region or data sources. For example, data are presented for the size, sex, and age distribution of the population. Where relevant, providing complete referencing details to original data collection procedures or sources is adequate.
?	Unclear or incomplete description of geographical area, its residents and hospitals or data sources used.
-	No description of investigated area
B – Quality of description of included population	
+	Clear description of in- and exclusion criteria are presented. Minimal criteria were considered sex, age and reason for amputation (the level of amputation is addressed separately.)
?	Unclear or incomplete description of in- and exclusion criteria
-	No description of in- and exclusion criteria
C – Quality of description of level of amputation	
+	Clear description of the levels of amputation in line with international guidelines or codes, and a clear definition of whether amputations were the first, recurrent or any in sequence.
?	Unclear or incomplete description of levels of amputation in line with international guidelines or codes, or unclear or incomplete definition of sequence of amputation.
-	No description of levels of amputation or sequence of amputation.
D – Quality of information source	
+	Source of information was complete, may include a combination of national health statistics and hospital records. Is information provided for when time to death was measured from – being admission, operation or discharge? Are the number of individuals at each stage of study reported – including number potentially eligible, number included, and number completed to follow-up? Were the number without an alive/death status identified?
?	Only national health statistics used, missing information for relevant time points.
-	Poor or no description given on data sources and missing all important information

Table 2: Study and population characteristics of included studies reporting 30-day mortality after major lower limb amputation

Study			Population							
Setting, country	Author	Period	n	Levels included	Population	% DM	First or any	Age (years)[a]	Gender (% men)	Susceptibility to bias
ACS NSQIP; US	Easterlin, 2013 [4]	2005-2009	9244	TT; KD; TF	Excluded DNR/ terminal	62	Any	66	62	+ + - ?
	Iannuzzi, 2013 [16]	2005-2010	11038	TT; TF	All, no further description	-	-	-	61	+ - - ?
	Karam, 2013 [18]	2005-2008	6839	BK; AK	All, no further description	61	-	67% aged >60 years	62	+ - ? ?
	Davenport, 2012 [19]	2005-2009	6188	TT; TF	DM and/or PAD only	9 [b]	Any	67 (14)	61	+ + + +
	Nelson, 2012 [20]	2005-2010	9368	TT; TF	All	TT: 69 TF: 52	-	TT: 65 TF: 70	TT: 66 TF: 55	+ + - ?
	Belmont, 2011 [21]	2005 – 2008	2911	TT	-	68	Any	66 (14)	64	+ + + ?
Medicare; US	Jones, 2013 [22]	2000-2008	186338	AD; TT; KD; TF; HD	PAD	60	First in period	79 (8) (65- excl.)	48	+ + + ?
Hospitals, NL	Fortington, 2013 [3]	2003-2004	299	TT; KD; TF	Vascular, infection and/or DM	51	First	74 (11)	56	+ + + +
Health insurance; Germany	Icks, 2011 [1]	2004-2007	444	PF/A; TT; KD; TF; HD	All, no further description	58	First	69 (12)	71	? ? + ?
HES; England	Vamos, 2010 [11]	P1: 2000-2001; P2: 2004-2005	P1: - P2: 4424 [c]	TA; TT; KD; TF; HD	Excluded trauma	DM1 P1: - P2: 8 DM2 P1: - P2: 32	Any	P1: - P2: 76 [IQR: 62-80]	P1: - P2: 67	+ + + +
Statewide hospital database; USA	Sandnes, 2004 [10]	P1: 1987-1989; P2: 1990-1994; P3: 1995-2000	9373 [d]	TT; TF	Excluded cancer, trauma, and aged <18 years	TT: 63 TF: 54	Last in period	TT: 68 (15) TF: 75 (14)	TT: 62 TF: 51	+ + + +
Veterans Health Administration; US	Mayfield, 2001 [23]	1992	2946 [c]	TT; KD; TF	Excluded cancer and trauma	-	Most proximal	66 (range 24-104)	TT: 7 TF: 11	+ + + +
VA NSQIP; US	Feinglass, 2001 [24]	Oct 1991- Sept 1995	4061	TT; TF	Excluded aged <40	TT: 63 TF: 39	First	TT: 66 TF: 70	100	+ + + ?

Note: ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program; DM = Diabetes Mellitus; DM1 = Type 1 DM; DM2 = Type 2 DM; PAD = peripheral artery disease; DNR = do not resuscitate; term = terminal cancer or chemotherapy; HES = Hospital Episode Statistics; NIS = Nationwide Inpatient Sample; VA = Veteran's affairs; US = United States of America; NL = the Netherlands; PF/A = amputation distal to and including ankle; AD = ankle disarticulation; TT = transtibial; U-TT = unilateral TT; KD = knee disarticulation; TF = transfemoral; U-TF = unilateral TF; HD = hip disarticulation; BK = below knee; AK = above knee; P1 = period 1; P2 = period 2; P3 = period 3. -: information not presented, not presented for the whole population or includes population that were excluded. [a]: mean (standard deviation) unless indicated otherwise; [b]: number of patients with postoperative ICD-9 code representing DM, however, other codes (e.g. gangrene/sepsis or arterial disease) may also contain people with DM, but that information is not presented; [c]: mortality presented for number of amputations, not number of patients ; [d]: only data from this study on patients with major amputation, patients with toe or transmetatarsal amputation excluded.

Table 3: 30-day mortality (in %) after major lower limb amputation

Setting, country	Author	all	TT	TF	Difference	DM	NoDM	Difference
ACS NSQIP; US	Easterlin, 2013 [4]	8	-	-	-	8	9	1
	Iannuzzi, 2013 [16]	9	-	-	-	-	-	-
	Karam, 2013 [18]	9	**7**	**13**	**6**	9	10	1
	Davenport, 2012 [19]	8	**-**	**-**	**-**	-	-	-
	Nelson, 2012 [20]	-	**7**	**13**	**6**	TT: 6 TF: 14	-	-
	Belmont, 2011 [21]	7	-	-	-	-	-	-
Medicare; US	Jones, 2013 [22]	14	-	-	-	-	-	-
Hospitals; NL	Fortington, 2013 [3]	22	17	22	5	22	20	2
Health insurance; Germany	Icks, 2011 [1]	-	-	-	-	**10**	**19**	**9**
HES; England	Vamos, 2010 [11]	P1: 14 P2: 13	-	-	-	P1: 13 P2: 9 (DM1) P1: 13 P2: 14 (DM2)	P1: 14 P2: 13	P1: 1 P2: 4
Statewide hospital databases; US	Sandnes, 2004 [10]	-	P1: 10 P2: 7 P3: 6	P1: 16 P2: 16 P3: 14	P1: 6 P2: 9 P3: 8			
Veteran's health administration	Mayfield, 2001 [23]	-	7	11	4	-	-	-
VA NSQIP; US	Feinglass, 2001 [24]	-	**6**	**13**	**7**	-	-	-

Note: numbers are percentages; ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program; DM = Diabetes Mellitus; DM1 = Type 1 DM; DM2 = Type 2 DM; HES = Hospital Episode Statistics; TT = transtibial amputation; TF = transfemoral amputation; VA = Veteran's affairs; US = United States of America; NL = the Netherlands; UK = United Kingdom; P1 = period 1; P2 = period 2; P3 = period 3. **Bold** text indicates that a significant difference between groups was reported by the authors.

Table 4: Study and population characteristics of included studies reporting in-hospital mortality after major lower limb amputation

Study			Population								
Setting, country	Author	Period	n	Levels included	Population	% with DM	First or any	Age (years) [a]	Gender (% men)	Length of stay	Susceptibility to bias
Spain	Lopez de Andres, 2015 [25]	2001-2012	64710 [b]	TT; KD; TF; HD	Trauma excluded	DM1: 2 DM2: 54	Any	DM1: 65 DM2: 74 NoDM: 71	DM1: 64 DM2: 63 NoDM: 70	DM1: 18 DM2: 17 NoDM: 17 (median)	? + + +
Taiwan	Mao, 2014 [26]	1997-2010	BK: 952 AK: 168	BK; AK	PAD only	BK: 89 AK: 70	-	BK: 70 AK: 74	BK: 57 AK: 61	-	? ? ? +
Germany	Malyar, 2013 [27]	2005 2007 2009	05: 18494 07: 16322 09: 16724	TT; KD; TF; HD	PAD only	-	Any	-	-	-	+ ? ? +
ACS NSQIP; US	Easterlin, 2013 [4]	2005-2009	9244	TT; KD; TF	Excluded DNR/ term	62	Any	66	62	-	+ + - +
	Davenport, 2012 [19]	2005-2009	6188	TT; TF	DM and/or PVD only Excluded DNR/term	9 [c]	Any	67 (14)	61	2005: 12 days 2009: 9 days (median)	+ + + +
HES, England	Moxey, 2012 [2]	2002-2006	14168	TT; KD; TF	Trauma or malignancy excluded	44	Any	70	66	22 days (median)	+ ? + +
	Moxey, 2010 [28]	2003-2008	25578 [b]	TT; KD; TF	All	39	Any	-	-	-	+ ? + +
Illinois non federal hospitals, US	Feinglass, 2008 [9]	1987-2004	28042 [d]	TT; TF (KD, HD excluded)	Trauma, malignancy, aged <35 excluded	62	Any	TT: 69 (13) TF: 75 (12)	50	-	+ + + +
Veterans Health Administration, US	Bates, 2006 [29]	1 Oct 2002 – 30 Sept 2003	2375	TT; TF; HD	All	DM1: 18 DM2: 65	Not in prior 12 months	67 (11)	99	28.6 (52.3)	? + + +
VA Patient Treatment File, US	Kazmers, 2000 [30]	1991-1994	8696	TT; TF	Circulatory system disorders	-	Any	68 (10)	-	TT: 32.0 (28.3) TF: 28.2 (31.1) both:49.8 (38.0) [e]	+ ? ? +

Note: ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program; DM = Diabetes Mellitus; DM1 = Type 1 DM; DM2 = Type 2 DM; PAD = peripheral artery disease; DNR = do not resuscitate; term = terminal cancer or chemotherapy; HES = Hospital Episode Statistics; VA = Veteran's affairs; US = United States of America; TT = transtibial; KD = knee disarticulation; TF = transfemoral; HD = hip disarticulation; BK = below knee; AK = above knee; -: information not presented, not presented for the whole population or includes population that were excluded; [a]: mean (standard deviation); [b]: procedures, not number of patients; [c]: number of patients with postoperative ICD-9 code representing DM, however, other codes (e.g. gangrene/sepsis or arterial disease) may also contain people with DM, but that information is not presented. [d]: only data from this study on patients with amputation at the levels TT and TF included; [e]: 'both' concerns patients who underwent both TT and TF during the same hospital stay, without information on the most proximal amputation being ipsi- or contralateral.

Table 5: In-hospital mortality (in %) after major lower limb amputation

Setting, country	Author	All	TT	TF	Difference	DM	No DM
Spain	Lopez de Andres, 2015 [25]	-	-	-	-	DM1: 8.9 DM2: 10.1	No DM: 13.6
Taiwan	Mao, 2014 [26]	-	**4**	**12**	**8**	-	-
Germany	Malyar, 2013 [27]	05: 20 07: 20 09: 19	-	-	-	-	-
ACS NSQIP; US	Easterlin, 2013 [4]	5	-	-	-	-	-
	Davenport, 2012 [19]	4	-	-	-	-	-
HES; England	Moxey, 2012 [2]	17	*	*	*	**	**
	Moxey, 2010 [28]	17	12	22	10	-	-
Illinois non federal hospitals, US	Feinglass, 2008 [9]	8	6	11	5	-	-
Veterans Health Administration, US	Bates, 2006 [29]	8	**5**	**12**	**7**	DM1: 8 DM2: 6	-
VA Patient Treatment File; US	Kazmers, 2000 [30]	13	**10**	**17**	**7**	-	-

Note: numbers are percentages or Odd's ratios and 95% confidence intervals; ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program; DM = Diabetes Mellitus; DM1 = Type 1 DM; DM2 = Type 2 DM; HES = Hospital Episode Statistics; TT = transtibial amputation; TF = transfemoral amputation; VA = Veteran's affairs; US = United States of America; **Bold** text indicates that a significant difference between groups was reported by the authors. *: Odd's ratios (95%CI) of mortality for TF vs TT were 1.52 (1.28-1.80) for women and 1.48 (1.30-1.68). **: Odd's ratios (95%CI) of mortality for DM vs noDM were 0.58 (0.49-0.70) for women and 0.55 (0.48-0.63) for men.

Figure 1: PRISMA flow chart