High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease

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Background Little is known regarding the contemporary outcomes of older patients with peripheral artery disease (PAD) undergoing major lower extremity (LE) amputation in the United States. We sought to characterize clinical outcomes and factors associated with outcomes after LE amputation in patients with PAD.

Methods Using data from the Centers for Medicare and Medicaid Services from January 1, 2000, to December 31, 2008, we examined the national patterns of mortality after major LE amputation among patients 65 years or older with PAD. Cox proportional hazards models were used to investigate the association between clinical variables, comorbid conditions, year of index amputation, geographic variation, and major LE amputation.

Results Among 186,338 older patients with identified PAD who underwent major LE amputation, the mortality rate was 13.5% at 30 days, 48.3% at 1 year, and 70.9% at 3 years. Age per 5-year increase (hazard ratio [HR] 1.29, 95% CI 1.29-1.29), history of heart failure (HR 1.71, 95% CI 1.71-1.72), renal disease (HR 1.84. 95% CI 1.83-1.85), cancer (HR 1.71, 95% CI 1.70-1.72), and chronic obstructive pulmonary disease (HR 1.33, 95% CI, 1.32-1.33) were all independently associated with death after major LE amputation. Subjects who underwent above knee amputation had a statistically higher hazard of death when compared with subjects who underwent LE amputation at more distal locations (HR with above the knee amputation 1.31, 95% CI 1.25-1.36).

Conclusions Older patients with PAD undergoing major LE amputation still face a slightly high mortality risk, with almost half of all patients with PAD dying within a year of major LE amputation. (Am Heart J 2013;165:809-815.e1.)

Major nontraumatic amputation of the lower extremity (LE) is a commonly performed procedure in patients with peripheral artery disease (PAD).[1–3] Based on American College of Cardiology/American Heart Association guideline recommendations, major LE amputation is generally reserved for patients without medical or revascularization options because LE amputation is associated with significant mortality, morbidity, and health care costs.[1,4,5] However, these data come from studies that are over-a-decade out of date, and little is known about the contemporary clinical outcomes in patients with PAD who undergo major LE amputation. Although quality improvement has been linked to a significant change in patient outcomes in myocardial infarction (MI), stroke, and congestive heart failure, little focus has been placed on patients with PAD. In fact, the performance of major LE amputation varies based on a number of factors including patient-specific factors, geographic region, and time, but no comprehensive report has evaluated the effect of these factors on cardiovascular outcomes in patients after major LE amputation.[3,6,7]

To address these needs, we performed an analysis of US Medicare data to provide a current report of outcomes in patients with PAD after major LE amputation. Our specific aims were to (1) characterize rates of death, MI, and stroke in patients with PAD after major LE amputation; (2) determine factors associated with clinical outcomes after major LE amputation; (3) determine if there was a geographic variation in outcomes after major LE amputation across the United States; and (4) determine if outcomes after major LE amputation varied over time.

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Table I. Demographic and clinical characteristics

	Overall (n = 2,730,742)	PAD without LE amputation (n = 2,544,404)	PAD with LE amputation (n = 186,338)	*P*
Age (y), mean ± SD	77.4 ± 7.6	77.3 ± 7.5	78.5 ± 8.2	<.001
Age (y)				
65-69	490,087 (17.9)	459,538 (18.1)	30,549 (16.4)	<.001
70-74	559,312 (20.5)	524,965 (20.6)	34,347 (18.4)	<.001
75-79	627,886 (23.0)	589,502 (23.2)	38,384 (20.6)	<.001
≥80	1,053,457 (38.6)	970,399 (38.1)	83,058 (44.6)	<.001
Male	1,352,662 (49.5)	1,263,035 (49.6)	89,627 (48.1)	.001
Race				
White	2,342,742 (85.8)	2,217,917 (87.2)	124,825 (67.0)	<.001
Black	293,285 (10.7)	240,874 (9.5)	52,411 (28.1)	<.001
Asian	17,483 (0.6)	16,417 (0.6)	1066 (0.6)	<.001
Other	77,232 (2.8)	69,196 (2.7)	8036 (4.3)	<.001
US geographic region				
New England	132,094 (4.8)	124,789 (4.9)	7305 (3.9)	.672
Middle Atlantic	406,576 (14.9)	381,189 (15.0)	25,387 (13.6)	<.001
South Atlantic	595,493 (21.8)	550,437 (21.6)	45,056 (24.2)	<.001
East North Central	525,337 (19.2)	494,627 (19.4)	30,710 (16.5)	<.001
East South Central	217,045 (7.9)	198,798 (7.8)	18,247 (9.8)	<.001
West North Central	195,749 (7.2)	184,858 (7.3)	10,891 (5.8)	<.001
West South Central	333,659 (12.2)	306,032 (12.0)	27,627 (14.8)	<.001
Mountain	104,083 (3.8)	98,350 (3.9)	5733 (3.1)	<.001
Pacific	220,706 (8.1)	205,324 (8.1)	15,382 (8.3)	.005
Comorbidities				
Cancer	236,135 (8.6)	223,021 (8.8)	13,114 (7.0)	<.001
Cerebrovascular disease	436,161 (16.0)	388,865 (15.3)	47,296 (25.4)	<.001
Congestive heart failure	987,779 (36.2)	895,135 (35.2)	92,644 (49.7)	<.001
Chronic obstructive pulmonary disease	973,553 (35.7)	907,824 (35.7)	65,729 (35.3)	<.001
CAD	1,674,727 (61.3)	1,571,028 (61.7)	103,699 (55.7)	<.001
Dementia	97,360 (3.6)	79,930 (3.1)	17,430 (9.4)	<.001
Diabetes mellitus	1,021,469 (37.4)	909,131 (35.7)	112,338 (60.3)	<.001
Hypertension	2,107,597 (77.2)	1,958,113 (77.0)	149,484 (80.2)	<.001
Renal disease	448,747 (16.4)	393,778 (15.5)	54,969 (29.5)	<.001

Methods

Data sources

We obtained the 100% inpatient Medicare standard analytic files and corresponding denominator files from the Centers for Medicare and Medicaid Services from January 1, 2000, through December 31, 2008. The inpatient files contain institutional claims for facility costs covered under Medicare Part A. The denominator files contain beneficiary demographic and clinical characteristic data. We restricted the study population to those patients with fee-for-service Medicare Part A and B enrollment at the index admission and censored patients if they switched to managed care and/or dropped Medicare Part A or B.

Identification of patients

We identified beneficiaries for whom an *International Classification of Diseases, Ninth Revision* (ICD-9-CM) diagnosis code or procedure code for LE PAD was reported during the study period (online Appendix A). After selecting this PAD cohort, we then identified those beneficiaries who underwent a first major LE amputation during the study period as those for whom an *ICD-9-CM* procedure code (84.13-84.18) for above knee or below knee amputation was reported. In subjects who underwent multiple LE amputations, those that occurred after the index major amputation were not included in the analysis.

Patient characteristics

Patient demographic characteristics included age, sex, race, state of residence, and zip code of residence. Medicare beneficiaries report race at the time of enrollment. We used previously validated methods to identify comorbid conditions using *ICD-9* billing claims for up to 5 years before the index hospitalization.[8] We used the admission date and discharge date from the index hospitalization to calculate the length of stay (LOS). We used the patient's state of residence to group beneficiaries into 9 US Census Bureau regions (online Appendix B).

Statistical analysis

We present categorical variables as frequencies with percentages and continuous variables as means with SDs. To test for differences between groups, we used the Pearson χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables. Cox proportional hazards models were created to show the hazard ratios (HRs) associated with LE amputation and clinical variables, comorbid conditions, year of index amputation, and geographic variation.

The Duke University institutional review board reviewed and approved this study design. We used SAS statistical software, version 9.2 (SAS Institute Inc, Cary, NC) for all analyses.

Table II. Rate of death, MI, and stroke after major LE amputation during the study period

Event	From index procedure to event	All (n = 2,730,742)			PAD without LE amputation (n = 2,544,404)			PAD with LE amputation (N = 186,338)			*P* value, comparing PAD without LE amputation vs PAD with LE amputation
		Rate (%)	95% Lower limit (%)	95% Upper limit (%)	Rate (%)	95% Lower limit (%)	95% Upper limit (%)	Rate (%)	95% Lower limit (%)	95% Upper limit (%)	
All-cause mortality	1 mo	7.4	7.4	7.4	6.9	6.9	7.0	13.5	13.3	13.6	<.001
	1 y	25.9	25.8	25.9	24.2	24.2	24.3	48.3	48.1	48.6	
	2 y	36.2	36.2	36.3	34.4	34.3	34.4	61.4	61.1	61.6	
	3 y	45.1	45.0	45.1	43.2	43.1	43.2	70.9	70.6	71.1	
MI	1 mo	1.9	1.9	1.9	1.9	1.9	1.9	1.2	1.1	1.2	<.001
	1 y	6.0	6.0	6.0	6.0	6.0	6.1	5.0	4.9	5.1	
	2 y	8.7	8.7	8.7	8.8	8.8	8.8	7.3	7.2	7.4	
	3 y	10.9	10.8	10.9	11.0	11.0	11.1	8.9	8.8	9.1	
Stroke	1 mo	1.7	1.7	1.7	1.8	1.8	1.8	1.0	0.9	1.0	<.001
	1 y	6.6	6.6	6.7	6.8	6.8	6.8	4.3	4.2	4.4	
	2 y	9.7	9.7	9.7	9.9	9.9	10.0	6.2	6.1	6.3	
	3 y	12.1	12.0	12.1	12.4	12.4	12.4	7.5	7.4	7.7	

Responsibility

This project was funded, in part, by internal support from the Duke Clinical Research Institute. This project was also supported on infrastructure provided by cooperative agreement number U19HS021092 from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

Patient characteristics

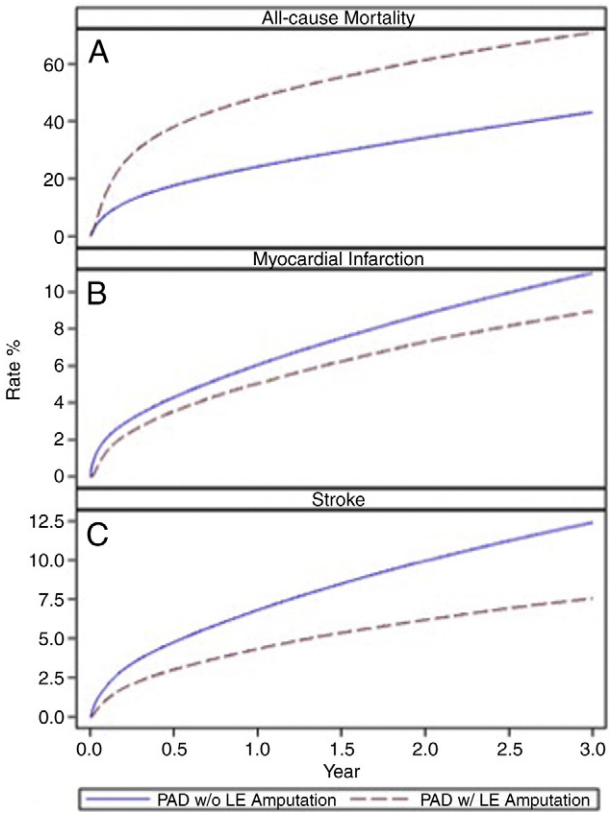
There were nearly 3 million Medicare beneficiaries hospitalized for PAD from 2000 through 2008. A total of 186,338patients (6.8% of the PAD group) underwent major LE amputation during the study period. Table I shows the demographic and clinical characteristics of all Medicare beneficiaries who were hospitalized for PAD and the characteristics of those with and without major LE amputation during the study period.

Among beneficiaries who underwent major LE amputation, nearly 60% were older than 75 years and nearly half were men. Patients with PAD who underwent major LE amputation were more likely to be black (28.1% vs 9.5%, $P < .001$), have diabetes mellitus (60.3% vs 35.7%, $P < .001$), and have renal disease (29.5% vs 15.5%, $P < .001$), when compared with patients with PAD who did not undergo major LE amputation.

Clinical outcomes

The median (25th, 75th percentile) follow-up for all patients in this study was 681 days (205 days, 1332 days).

Figure 1



The occurrence of death, MI, and stroke in patients hospitalized for PAD with and without major LE amputation: cumulative incidence rates of all-cause mortality (A), MI (B), and stroke (C) after major LE amputation.

Table III. Factors associated with death after major amputation of the LE

Label	HR	95% Lower confidence limit for HR	95% Upper confidence limit for HR	χ^2	P
Age per 5-y increase	1.29	1.29	1.29	189,555.2	<.001
History of congestive heart failure	1.71	1.71	1.72	86,472.9	<.001
History of renal disease	1.84	1.83	1.85	75,123.7	<.001
History of cancer	1.71	1.70	1.72	39,784.5	<.001
History of chronic obstructive pulmonary disease	1.33	1.32	1.33	26,202.0	<.001
History of hypertension	0.80	0.79	0.80	13,234.0	<.001
History of diabetes mellitus	1.22	1.22	1.23	12,978.1	<.001
History of dementia	1.53	1.52	1.54	12,463.4	<.001
Year	0.96	0.96	0.96	11363.1	<.001
History of cerebrovascular disease	1.22	1.22	1.23	8566.8	<.001
History of CAD	0.89	0.88	0.89	4633.1	<.001
Male	1.09	1.08	1.09	2422.7	<.001
Race					
Black	1.05	1.05	1.06	338.1	<.001
Other	0.96	0.95	0.97	53.2	<.001
Asian	0.94	0.92	0.96	37.3	<.001

From 2000 through 2008, the 30-day, 1-year, and 3-year overall mortality rates after major LE amputation were 13.5%, 48.3%, and 70.9%, respectively. Rates of MI and stroke at 30 days, 1 year, and 3 years are also shown in Table II and Figure 1. When compared with patients with PAD who did not undergo major LE amputation, patients with major LE amputation had significantly higher rates of mortality at 30 days, 1 year, and 3 years (Table II and Figure 1). Rates of MI and stroke were lower in patients with PAD after major LE amputation compared with those without LE amputation. Length of stay during the index hospitalization was substantially longer in patients with PAD who underwent major LE amputation (LOS [days] ± SD 13.2 ± 13.0) when compared with patients with PAD who did not undergo major LE amputation (LOS [days] ± SD 6.0 ± 7.5, $P < .001$).

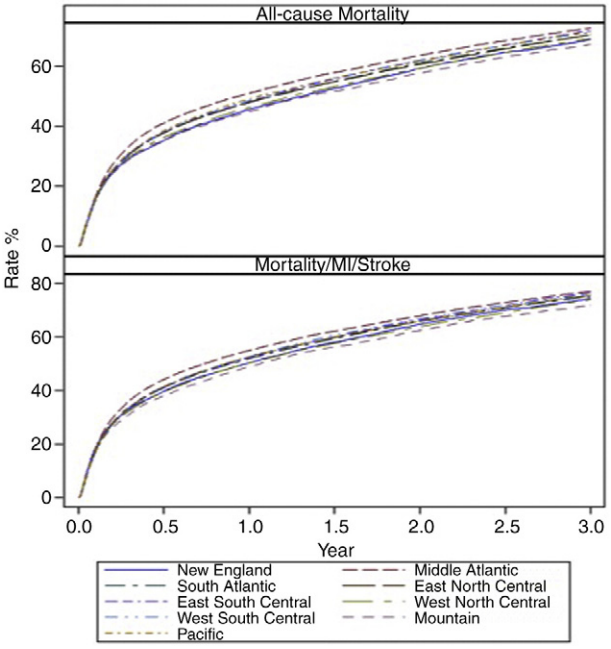
Clinical factors associated with mortality after major LE amputation

Table III shows the results of Cox models created to show the clinical predictors of death after major LE amputation. Age per 5-year increase, history of heart failure, renal disease, cancer, and chronic obstructive pulmonary disease were independently associated with death after major LE amputation. A history of coronary artery disease (CAD) and hypertension were associated with reduced risk of death after major LE amputation.

Temporal trends in mortality after major LE amputation

The adjusted HR of death after major LE amputation per year after 2000 was 0.958 (95% CI 0.957-0.959, $P < .001$) (Table III). The 30-day and 1-year mortality rates for patients undergoing major LE amputation in 2000 were 13.8% and 47.8%, whereas the 30-day and 1-year mortality rates for patients undergoing the same procedure in 2008 were 12.7% and 47.7%.

Figure 2

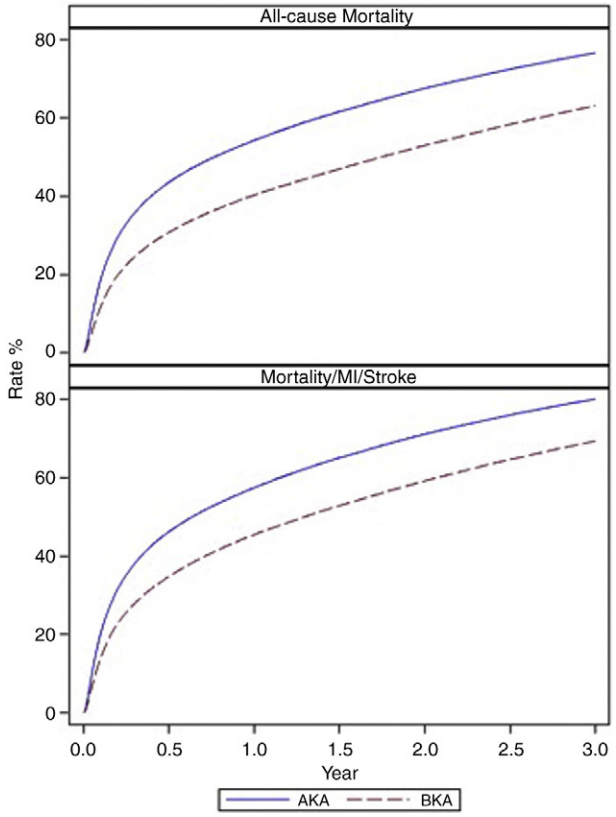


Geographic variation in the occurrence of death after major LE amputation: unadjusted cumulative incidence rates of all-cause mortality and mortality/MI/stroke after major LE amputation according to US Census Bureau regions.

The effect of geography on mortality after major LE amputation

Geographic variation was also independently associated with death after major LE amputation after adjusting for clinical variables and temporal trends. Figure 2 shows

Figure 3



The effect of level of amputation on the occurrence of death after major LE amputation: cumulative incidence rates of all-cause mortality and mortality/MI/stroke according to level of amputation (AKA, BKA). BKA, below the knee amputation.

the unadjusted rates of all-cause mortality and mortality/MI/stroke according to US Census Bureaus after major LE amputation. Death after major LE amputation occurred more frequently in the Pacific region (adjusted HR 1.048, 95% CI 1.041-1.056, $P < .001$) and less frequently in the West South Central region (adjusted HR 0.943, 95% CI 0.936-0.950, $P < .001$) when compared with the South Atlantic region as reference.

The effect of level of amputation on mortality after LE amputation

The performance of above the knee amputation (AKA) was associated with a statistically significant higher hazard of death when compared with more distal LE amputation locations (HR for AKA 1.30, 95% CI 1.25-1.36, $P < .001$). As shown in Figure 3, 3-year mortality rates were 76.6% in patients undergoing AKA, whereas 3-year mortality rates were 63.1% in patients undergoing below the knee amputation.

Discussion

Our study demonstrates that in contemporary clinical practice, older Medicare beneficiaries with PAD (with and without major LE amputation) continue to face very high short- and long-term mortality rates. As expected, advanced age, history of heart failure, renal failure, cancer, and chronic obstructive pulmonary disease were all independent predictors of mortality after major LE amputation. These findings have important implications for health policy, clinical care, and patient awareness.

In those patients who underwent major LE amputation, mortality rates were double those in patients who did not undergo LE amputation at 30 days (death rate: LE amputation 13.5% vs no LE amputation 6.9%, $P < .001$) and 1 year (death rate: LE amputation 48.3% vs no LE amputation 24.2%, $P < .001$). This difference remained dramatically higher at 3 years (death rate: LE amputation 70.9% vs no LE amputation 43.2%, $P < .001$). The factors associated with this higher mortality including advanced age, heart failure, renal disease, and cancer may have all contributed to these extremely high short- and long-term event rates after major LE amputation. The presence of CAD was associated with a lower risk of death after major LE amputation, potentially highlighting a finding from one of our prior observations in a Danish national registry that patients with clinically identified CAD and PAD are treated more aggressively with medical therapy than those patients with PAD alone.[9]

These data highlight the unacceptably high rates of mortality in patients with PAD with and without major LE amputation and provide focus for areas of further research and improvement. For clinicians, payers, and policy makers, awareness of the risk of mortality after major LE amputation may provide important opportunities for identification of these high-risk patients with PAD. Further study of this high-risk group of patients will be required to determine if (*a*) physician and patient education programs and/or aggressive revascularization efforts can help decrease or prevent major LE amputation, (*b*) care pathways can make major LE amputation procedures safer, and (*c*) evidence-based treatments for atherosclerosis (ie, antiplatelet agents and statins) or novel therapies can reduce mortality after major LE amputation. These comprehensive efforts have been successfully initiated in coordinated MI, heart failure, and stroke programs[10–12]; however, the recent American College of Cardiology/American Heart Association performance measures document for adults with PAD does not address patients at risk for or undergoing major LE amputation.[13] This strikingly high rate of mortality serves as a call to action for clinicians and researchers to both identify the cause of death in these patients and determine whether processes of care or novel treatment options can influence this mortality rate.

Prior studies of major LE amputation have reported a wide variation of mortality rates at 30 days (6.9%-30.0%)

and 1 year (30.3%-54.0%).[5,14–21] Although patient-specific factors are critical determinants of mortality after major LE amputation, 2 additional factors noted in this study, geographic variation and level of amputation, may have contributed to these prior, imprecise event rates. In the current study, both factors remain independent predictors of mortality after major LE amputation after statistical adjustment for baseline variables. When considered separately, the geographic variation observed in mortality rates highlights the need to better understand the impact of unmeasured contributors such as socioeconomic status, access to care, revascularization efforts, wound care, medical therapy, and patient education programs. For those regions with higher rates of mortality, it should also signal that lessons can be learned from regions with lower mortality and that improvement is needed. The significantly higher event rates in those patients requiring extensive amputation (ie, AKA) suggest that every opportunity should be taken to avoid AKAs. Furthermore, a uniform treatment algorithm to determine amputation level at the time of major LE amputation is needed, as much of the decision making about the level of amputation is determined by physician expertise and preference. As a whole, the significance of geographic variation and level of amputation emphasize the importance of developing standardized care pathways and quality initiatives before, during, and after major LE amputation.

An important point of encouragement in the midst of these exceedingly high mortality rates after major LE amputation is the decline in mortality over the study period. The 30-day mortality rates for patients undergoing major LE amputation in 2000 was 13.8%, whereas the 30-day mortality rates for patients undergoing the same procedure in 2008 was 12.6%. There are multiple potential explanations for this declining adjusted rate of mortality after major LE amputation during the study period. It is possible that patients with PAD were treated more aggressively for ischemic heart disease, a fact that may be corroborated by lower cumulative rates of stroke and MI in the amputation cohort. Unfortunately, we were unable to measure the intensity of medical therapy or revascularization in this inpatient Medicare data set. In addition, the implementation of perioperative surgical quality improvement programs in some centers may have influenced the 30-day mortality rates observed in our study.[22,23] Despite the decline in short-term mortality, the 1- and 3-year mortality rates are similar at the beginning and end of the study period and reflect no significant improvement over time.

The current study has multiple limitations. First, Medicare claims data do not include information regarding the duration, burden, or severity of disease that may affect the rate of major LE amputation and long-term outcomes after major LE amputation. Second, although Medicare Part A data capture inpatient hospital claims, it is possible that some patients with major LE amputation were not included in the current analysis. The use of inpatient claims made it impossible to fully investigate the use of diagnostic testing and revascularization, given a shift from inpatient to outpatient care. Finally, this analysis only included those patients enrolled in fee-for-service Medicare, and the generalizability to all US patients, including non–fee-for-service Medicare beneficiaries, those with private insurance, and younger patients, is unclear.

In conclusion, mortality rates after major LE amputation in patients with PAD remain high in the United States. Since 2000, there appears to have been a decline in the short-term mortality rate after major LE amputation in this population. Future registries and clinical trials should aim to identify both quality improvement programs and standard and novel treatments that decrease this unacceptably high mortality rate. Finally, there remains a critical need for education programs in the United States that focus on prevention, early diagnosis, and aggressive treatment for patients with PAD at high risk for major LE amputation and subsequent death.

Disclosures

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References

1. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006; 113(11):e463-654.
2. Goodney PP, Beck AW, Nagle J, et al. National trends in lower extremity bypass surgery, endovascular interventions, and major amputations. Vasc Surg 2009;50(1):54-60.
3. Margolis DJ, Hoffstad O, Nafash J, et al. Location, location, location: geographic clustering of lower-extremity amputation among Medicare beneficiaries with diabetes. Diabetes Care 2011;34(11): 2363-7.

4. Peacock JM, Keo HH, Duval S, et al. The incidence and health economic burden of ischemic amputation in Minnesota, 2005-2008. Prev Chronic Dis 2011;8(6):A141.
5. Cruz CP, Eidt JF, Capps C, et al. Major lower extremity amputations at a Veterans Affairs hospital. Am J Surg 2003;186(5):449-54.
6. Goodney PP, Travis LL, Nallamothu BK, et al. Variation in the use of lower extremity vascular procedures for critical limb ischemia. Circ Cardiovasc Qual Outcomes 2011;5:94-102.
7. Jones WS, Patel MR, Dai D, et al. Temporal trends and geographic variation of lower-extremity amputation in patients with peripheral artery disease: results from U.S. Medicare 2000-2008. J Am Coll Cardiol 2012;60:2230-6.
8. Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. Med Care 1998;36(1):8-27.
9. Subherwal S, Patel MR, Kober L, et al. Missed opportunities: despite improvement in use of cardioprotective medications among patients with lower-extremity peripheral artery disease, underuse remains. Circulation 2012;126(11):1345-54.
10. Wolf PA, Clagett GP, Easton JD, et al. Preventing ischemic stroke in patients with prior stroke and transient ischemic attack: a statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke 1999;30(9):1991-4.
11. Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. JAMA 2010; 303(17):1716-22.
12. Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA 2004;291(22):2727-33.
13. Olin JW, Allie DE, Belkin M, et al. ACCF/AHA/ACR/SCAI/ SIR/SVM/SVN/SVS 2010 performance measures for adults with peripheral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on performance measures, the American College of Radiology, the Society for Cardiac Angiography and Interventions, the Society for Interventional Radiology, the Society for Vascular Medicine, the Society for Vascular Nursing, and the Society for Vascular Surgery (Writing Committee to Develop Clinical Performance Measures for Peripheral Artery Disease). Circulation 2010;122(24): 2583-618.
14. Tentolouris N, Al-Sabbagh S, Walker MG, et al. Mortality in diabetic and nondiabetic patients after amputations performed from 1990 to 1995: a 5-year follow-up study. Diabetes Care 2004;27(7): 1598-604.
15. Schofield CJ, Libby G, Brennan GM, et al. Mortality and hospitalization in patients after amputation: a comparison between patients with and without diabetes. Diabetes Care 2006;29(10): 2252-6.
16. Aragon-Sanchez J, Hernandez-Herrero MJ, Lazaro-Martinez 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(1):16-23.
17. Abou-Zamzam Jr AM, Teruya TH, Killeen JD, et al. Major lower extremity amputation in an academic vascular center. Ann Vasc Surg 2003;17(1):86-90.
18. Ploeg AJ, Lardenoye JW, Vrancken Peeters MP. Contemporary series of morbidity and mortality after lower limb amputation. Eur J Vasc Endovasc Surg 2005;29(6):633-7.
19. Kazmers A, Perkins AJ, Jacobs LA. Major lower extremity amputation in Veterans Affairs medical centers. Ann Vasc Surg 2000;14(3): 216-22.
20. Aulivola B, Hile CN, Hamdan AD, et al. Major lower extremity amputation: outcome of a modern series. Arch Surg 2004;139(4): 395-9 [discussion 399].
21. Abola MT, Bhatt DL, Duval S, et al. Fate of individuals with ischemic amputations in the REACH Registry: three-year cardiovascular and limb-related outcomes. Atherosclerosis 2012;221(2):527-35.
22. Belmont Jr PJ, Davey S, Orr JD, et al. Risk factors for 30-day postoperative complications and mortality after below-knee amputation: a study of 2,911 patients from the national surgical quality improvement program. J Am Coll Surg 2011;213(3):370-8.
23. Feinglass J, Pearce WH, Martin GJ, et al. Postoperative and late survival outcomes after major amputation: findings from the Department of Veterans Affairs National Surgical Quality Improvement Program. Surgery 2001;130(1):21-9.

Appendix A. *ICD-9-CM* diagnosis code or procedure code used for inclusion of subjects in the current study

Diagnosis codes:
440.0, 440.2, 440.20, 440.21, 440.22, 440.23, 440.24, 440.3, 440.30, 440.31, 440.32
440.4
440.9
443.9
444.0, 444.2, 444.22, 444.8, 444.81
447.1
445.0, 445.02
250.7, 250.70, 250.71, 250.72, 250.73
707.1, 707.10, 707.11, 707.12, 707.13, 707.14, 707.15, 707.19

Procedure codes:
00.4, 00.40, 00.41, 00.42, 00.43, 00.44, 00.45, 00.46, 00.47, 00.48
38.08, 38.18, 38.38, 38.48, 38.68, 38.91
39.25, 39.29, 39.50, 39.90
99.10

Appendix B. US Census Bureau regions

Division I:
New England
Connecticut
Maine
Massachusetts
New Hampshire
Rhode Island
Vermont

Division 2:
Middle Atlantic
New Jersey
New York
Pennsylvania

Division 3:
East North Central
Indiana
Illinois
Michigan
Ohio
Wisconsin

Division 4:
West North Central
Iowa
Kansas
Minnesota
Missouri
Nebraska
North Dakota
South Dakota

Division 5:
South Atlantic
Delaware
District of Columbia
Florida
Georgia
Maryland
North Carolina
South Carolina
Virginia
West Virginia

Division 6:
East South Central
Alabama
Kentucky
Mississippi
Tennessee

Division 7:
West South Central
Arkansas
Louisiana
Oklahoma
Texas

Division 8:
Mountain
Arizona
Colorado
Idaho
New Mexico
Montana
Utah
Nevada
Wyoming

Division 9:
Pacific
Alaska
California
Hawaii
Oregon
Washington