

# Determinants of Long-Term Outcomes and Costs in the Management of Critical Limb Ischemia: A Population-Based Cohort Study

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**Background**—The optimal treatment for critical limb ischemia remains controversial owing to conflicting conclusions from previous studies.

**Methods and Results**—We obtained administrative claims on Medicare beneficiaries with initial critical limb ischemia diagnosis in 2011. Clinical outcomes and healthcare costs over 4 years were estimated among all patients and by first treatment (endovascular revascularization, surgical revascularization, or major amputation) in unmatched and propensity-score-matched samples. Among 72 199 patients with initial primary critical limb ischemia diagnosis in 2011, survival was 46% (median survival, 3.5 years) and freedom from major amputation was 87%. Among 9942 propensity-score-matched patients (8% rest pain, 26% ulcer, and 66% gangrene), survival was 38% with endovascular revascularization (median survival, 2.7 years), 40% with surgical revascularization (median survival, 2.9 years), and 23% with major amputation (median survival, 1.3 years;  $P < 0.001$  for each revascularization procedure versus major amputation). Corresponding major amputation rates were 6.5%, 9.6%, and 10.6%, respectively ( $P < 0.001$  for all pair-wise comparisons). The cost per patient year during follow-up was \$49 700, \$49 200, and \$55 700, respectively ( $P < 0.001$  for each revascularization procedure versus major amputation).

**Conclusions**—Long-term survival and cost in critical limb ischemia management is comparable between revascularization techniques, with lower major amputation rates following endovascular revascularization. Primary major amputation results in shorter survival, higher risk of subsequent major amputation, and higher healthcare costs versus revascularization. Results from this observational research may be susceptible to bias because of the influence of unmeasured confounders. (*J Am Heart Assoc.* 2018;7:e009724. DOI: 10.1161/JAHA.118.009724.)

**Key Words:** amputation • cost • critical limb ischemia • Medicare • peripheral artery disease • revascularization

Critical limb ischemia (CLI) represents the most advanced manifestation of peripheral artery disease and is categorized as ischemic rest pain, nonhealing ischemic ulceration, or gangrene. Patients with CLI often present with multilevel

peripheral artery disease that prevents the arterial supply from meeting the metabolic demands of tissue at rest. Prompt revascularization by endovascular or open surgical procedures is indicated following the diagnosis of CLI diagnosis to preserve the limb and maintain limb function.<sup>1</sup> However, management of CLI remains highly controversial, particularly when selecting an initial revascularization strategy. In an analysis of 7900 CLI patients from the Vascular Quality Initiative, 3-year survival was lower with endovascular versus surgical revascularization strategies (70% versus 78%).<sup>2</sup> In the First-Line Treatments in Patients With Critical Limb Ischemia (CRITISCH) registry of 1200 CLI patients, there was no difference in 1-year mortality or major amputation between revascularization methods.<sup>3</sup> The randomized BASIL (Bypass versus Angioplasty in Severe Ischaemia of the Leg) study also found no differences in long-term mortality or major amputation when comparing endovascular versus surgical revascularization.<sup>4</sup> Although primary major amputation for CLI is associated with impaired mobility, high cost, high risk of contralateral limb amputation, and poor prognosis,<sup>5,6</sup> this procedure may be indicated in some patients with cognitive impairment, nonambulatory status,

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Accompanying Tables S1, S2 and Figures S1 through S4 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009724>

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## Clinical Perspective

### What Is New?

- No study has reported long-term outcomes and costs by first major critical limb ischemia treatment with adjustment for patient characteristics.
- Long-term survival and cost are comparable between endovascular and surgical revascularization, with lower major amputation rates following endovascular revascularization.
- Compared with each revascularization approach, primary major amputation is associated with shorter survival time, higher risk of subsequent major amputation, and higher healthcare costs.

### What Are the Clinical Implications?

- Considerable efforts are needed to raise disease awareness, implement coding to better define and identify the disease, refine diagnostic algorithms, establish evidence-based treatment pathways, and address the high mortality rates associated with this diagnosis.

extensive comorbidities, extensive gangrene, or infection.<sup>7</sup> Overall, the optimal treatment for CLI and determinants of long-term results remain controversial, and the total costs of care are unclear to the vascular specialist. The purpose of this study was to report long-term outcomes and costs following initial CLI diagnosis, with comparisons among endovascular revascularization, surgical revascularization, or major amputation as first-line treatment among a contemporaneous cohort of Medicare beneficiaries.

## Methods

### Data Sources

We obtained administrative claims from 2010 to 2015 on all fee-for-service Medicare beneficiaries available from the Centers for Medicare & Medicaid Services. Medicare is the primary payer in nearly 75% of CLI-related hospitalizations<sup>8</sup>; thus, data derived from Medicare claims are representative of nation-wide CLI outcomes. Data for the current analysis included claims from Medicare fee-for-service parts A (hospital inpatient) and B (hospital outpatient). Cost analyses additionally utilized a 5% sample from the Carrier file, which contains final action fee-for-service claims deriving mainly from noninstitutional providers, such as physicians, physician assistants, clinical social workers, and nurse practitioners. The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results. Metro Health Hospital Institutional

Review Board (Wyoming, MI) reviewed and approved this research, and the requirement for informed consent was waived.

### Patient Population

The patient population included adult Medicare beneficiaries with a first-time CLI diagnosis (incident cases) arising from in- or outpatient care at a participating hospital. We identified patients with CLI using *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes. Critical limb ischemia diagnosis date was defined as the date of the first claim with primary diagnosis of atherosclerosis of native arteries of the extremities with rest pain (*ICD-9-CM* code 440.22), ulceration (*ICD-9-CM* code 440.23), or gangrene (*ICD-9-CM* code 440.24) or the date of the first CLI-related procedure (ie, endovascular revascularization, surgical revascularization, major [above ankle] amputation, or minor [below ankle] amputation) occurring up to 10 days preceding the first claim to allow for delayed diagnosis claim reporting following CLI intervention. Determination of primary CLI diagnosis was made if the diagnosis code was first- or second-listed to minimize the influence of unrelated confounding conditions. Patients were included if CLI diagnosis was made between January 1, 2011 and December 31, 2011, they had continuous coverage from January 1, 2010 to December 31, 2011, and they did not have a CLI diagnosis code in 2010 (eg, patients had no CLI diagnosis during at least the past 12 months). Utilization of a 12-month stable diagnosis period is common in Medicare claims analyses of CLI patients.<sup>9,10</sup> Patients were followed through September 30, 2015, which corresponds to the date of the transition from *ICD-9-CM* to *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* codes.

### Patient Characteristics

Demographic patient data included age, sex, and race. Comorbidities included hypertension, diabetes mellitus, coronary artery disease, chronic kidney disease, hyperlipidemia, and tobacco use history. Geography was reported by region (South, Midwest, Northeast, West, or Puerto Rico) and population density (urban/rural) of the center initially caring for the patient. Clinical presentation was categorized as ischemic rest pain, ischemic ulcer, or gangrene.

### Determination of First Major Treatment

Major treatment for CLI was defined as endovascular revascularization, surgical revascularization, or major (above the ankle) amputation. Utilization of major treatments

following CLI diagnosis was determined with a combination of *ICD-9-CM* and *Current Procedural Terminology (CPT)* procedure codes (Table S1). The first major treatment was reported as the first endovascular revascularization, surgical revascularization, or major amputation procedure, regardless of subsequent treatments. In patients who underwent multiple first major treatments during the same encounter, the most invasive treatment was used for classification where major amputation was considered most invasive and endovascular revascularization was considered least invasive.

## Outcomes

Main clinical outcomes were survival and major amputation through 4 years of follow-up. Healthcare costs were estimated from Medicare reimbursements for hospital inpatient, hospital outpatient, and physician/supplier services. Costs were adjusted to 2016 US dollars using the Medical Care component of the Consumer Price Index. In order to account for mortality rate differences among groups, costs were reported in patients who were alive at the start of each follow-up year regardless of vital status during that year.

## Statistical Analysis

Baseline characteristics were reported as mean and SD for continuous variables and counts and percentages for categorical variables. Time to first-event outcomes were analyzed using Kaplan–Meier methods, Cox proportional hazards regression, and the cumulative incidence function in the presence of competing risks. The cumulative event hazard was estimated with the Anderson and Gill extension to the Cox proportional-hazards model for recurrent events.<sup>11</sup> The Hochberg procedure was used to control the family-wise type I error rate at 5% for multiple comparisons. In each analysis, patients with no events were censored after 4 years' follow-up; thus, the maximum possible follow-up duration for each patient ranged from 3.75 to 4.0 years, depending on actual diagnosis date. The hazard ratio for survival and freedom from major amputation was estimated in a multivariable model where variable selection used backward elimination. Owing to the large sample size of this study, the model was further reduced using the generalized  $R^2$  statistic to identify the strongest predictors of outcomes.<sup>12</sup> Variables were retained in this reduced multivariable model if  $R^2$  decreased by at least 0.01 when removed. In order to compare patient outcomes and costs by first major treatment, propensity scores were estimated using multinomial logistic regression, which represented the probability of receiving each major treatment for each

patient. The covariates used to estimate propensity scores included all variables specified in the Patient Characteristics section and listed in Table 1. The trio of propensity scores were used to match like patients using a nearest neighbor approach without replacement, where caliper width was set at 0.09 (0.25 SDs of the propensity score).<sup>13,14</sup> Costs were adjusted for censoring using partitioned estimator methods.<sup>15</sup> Data were analyzed using SAS (v9.4; SAS Institute, Cary, NC) and Stata Statistical Software (Release 13.1; StataCorp LP, College Station, TX).

## Results

### Patient Characteristics and Major Treatments

Of approximately 36.5 million Medicare beneficiaries enrolled in 2011, 116 031 received a CLI diagnosis (0.32% prevalence), of which 96 628 had no CLI-related claim over the previous year (0.26% incidence). After excluding 24 429 cases without primary CLI diagnosis (ie, CLI not first- or second-listed diagnosis within claim), 72 199 incident cases of primary CLI were included in this study.

Baseline patient characteristics among the entire sample and according to first major treatment are described in Table 1. Mean patient age was  $74 \pm 12$  years, 52% were male, and predominant races were white (76%) and black (19%). Hypertension (73%), diabetes mellitus (54%), and coronary artery disease (48%) were the most common comorbidities. Clinical presentation was characterized by rest pain in 29%, ulcer in 45%, and gangrene in 25% of patients. Among patients undergoing primary major amputation, 30% did not receive a diagnosis of gangrene. The percentage of patients with gangrene was 36% for black, 36% for other race, and 22% for white ( $P < 0.001$  for white versus black and other races). Primary major amputation was performed more frequently ( $P < 0.001$ ) in patients of black race (10%) versus white (4%) and other races (5%).

A total of 46 795 (65%) patients received a major treatment during follow-up (median, 9 days from CLI diagnosis), where primary procedures were endovascular revascularization (40%), surgical revascularization (20%), or major amputation (6%). Multiple primary major treatments were performed during the same encounter in 2670 patients, most commonly endovascular and surgical revascularization (2541 patients). Subsequent major treatments were relatively common in patients first treated with endovascular (50% of patients) or surgical (44% of patients) revascularization, but not major amputation (21% of patients). The cumulative number of subsequent major treatments received during follow-up was 1.4 per patient with primary endovascular revascularization, 1.2 per patient with surgical revascularization, and 0.5 for major

**Table 1.** Baseline Characteristics of Medicare Eligible Patients Diagnosed With Critical Limb Ischemia in 2011 Categorized by First Major Treatment\*

Characteristic	All Patients	Patient Status By First Major Treatment				
		Alive w/o Major Treatment	Endovascular	Surgical	Major Amputation	Died w/o Major Treatment
No. of patients	72 199 (100)	11 465 (16)	28 530 (40)	14 283 (20)	3982 (6)	13 939 (19)
<b>Geography<sup>†</sup></b>						
<b>Region</b>						
South	29 721 (42)	4349 (40)	12 250 (44)	5713 (41)	2057 (53)	5352 (41)
Midwest	17 000 (24)	2637 (24)	7177 (26)	3390 (24)	703 (18)	3093 (23)
Northeast	13 802 (20)	2427 (22)	4756 (17)	3037 (22)	653 (17)	2929 (22)
West	9204 (13)	1356 (13)	3795 (14)	1916 (14)	365 (9)	1772 (13)
Puerto Rico	340 (<1)	50 (<1)	93 (<1)	39 (<1)	90 (2)	68 (<1)
<b>Population density</b>						
Urban	62 623 (89)	9643 (89)	25 339 (90)	12 715 (90)	3345 (86)	11 581 (88)
Rural	7444 (11)	1176 (11)	2732 (10)	1380 (10)	523 (14)	1633 (12)
<b>Demographics</b>						
Male sex	37 681 (52)	5479 (48)	14 773 (52)	8281 (58)	2107 (53)	7041 (51)
Age, y	74±12	71±12	74±11	72±11	76±12	78±11
<b>Race</b>						
White	54 617 (76)	8601 (75)	21 374 (75)	11 290 (79)	2426 (61)	10 926 (79)
Black	13 476 (19)	2164 (19)	5346 (19)	2352 (17)	1340 (34)	2274 (16)
Other/unknown	4106 (6)	649 (6)	1723 (6)	599 (4)	209 (5)	698 (5)
<b>Medical history</b>						
Hypertension	53 046 (73)	8217 (72)	21 205 (74)	10 333 (72)	2937 (74)	10 354 (74)
Diabetes mellitus	38 823 (54)	5420 (47)	16 776 (59)	6798 (48)	2268 (57)	7561 (54)
Coronary artery disease	34 570 (48)	4059 (35)	14 440 (51)	7027 (49)	1854 (47)	7190 (52)
Chronic kidney disease	23 672 (33)	2378 (21)	10 162 (36)	3853 (27)	1507 (38)	5772 (41)
Hyperlipidemia	19 134 (27)	3064 (27)	7775 (27)	4059 (28)	808 (20)	3428 (25)
Smoking	14 481 (20)	1753 (15)	5754 (20)	4180 (29)	777 (20)	2017 (14)
<b>Clinical presentation</b>						
Rest pain	21 298 (29)	4339 (38)	8365 (29)	5977 (42)	276 (7)	2341 (17)
Ulcer	32 493 (45)	5568 (49)	13 625 (48)	4786 (34)	906 (23)	7608 (55)
Gangrene	18 408 (25)	1558 (14)	6540 (23)	3520 (25)	2800 (70)	3990 (29)

w/o indicates without.

\*Values are mean±SD or count (percentage).

<sup>†</sup>Data available in 70 067 patients.

amputation. Throughout the follow-up period, 33% of patients underwent a single revascularization procedure, 27% underwent multiple revascularizations, 9% received a single major amputation, and 1% received multiple major amputations. Among patients who underwent major amputation at any time in follow-up, 51% did not undergo previous revascularization, 25% underwent 1 previous revascularization procedure, and 24% underwent multiple previous revascularization procedures. Among patients not

receiving a major treatment, 45% were alive throughout the follow-up period and 55% died during follow-up.

### Clinical Outcomes

Over 4 years follow-up, survival was 46% (median survival, 3.5 years) and freedom from major amputation was 87% (Figures S1 and S2). In multivariate models of the association of baseline variables on risk of mortality and major

**Table 2.** Multivariate Analysis of Mortality and Major Amputation Risk Following Diagnosis of Critical Limb Ischemia\*

Characteristic	Mortality	Major Amputation
<b>Multivariate model</b>		
<b>Age, y</b>		
<50	1.0 (Ref.)	1.0 (Ref.)
50 to 59	1.33 (1.22, 1.44)	1.49 (1.28, 1.73)
60 to 69	1.53 (1.41, 1.65)	1.34 (1.17, 1.54)
70 to 79	2.02 (1.87, 2.18)	1.39 (1.21, 1.61)
80 to 89	3.22 (2.98, 3.49)	1.70 (1.48, 1.97)
≥90	5.49 (5.05, 5.97)	2.12 (1.81, 2.49)
<b>Clinical presentation</b>		
Rest pain	1.0 (Ref.)	1.0 (Ref.)
Ulcer	1.55 (1.51, 1.59)	1.41 (1.31, 1.52)
Gangrene	2.35 (2.28, 2.42)	5.21 (4.87, 5.57)
<b>Medical history</b>		
Chronic kidney disease	1.71 (1.68, 1.75)	1.14 (1.09, 1.20)
Coronary artery disease	1.27 (1.24, 1.30)	1.09 (1.04, 1.14)
Smoking	1.18 (1.15, 1.22)	1.34 (1.26, 1.41)
Diabetes mellitus	1.09 (1.06, 1.11)	†
Renal insufficiency	1.08 (1.05, 1.12)	†
Male sex	1.06 (1.04, 1.08)	†
Rural geography	1.06 (1.02, 1.09)	1.19 (1.11, 1.28)
Hypertension	0.90 (0.88, 0.92)	†
Hyperlipidemia	0.86 (0.84, 0.88)	0.85 (0.81, 0.90)
<b>Region</b>		
Midwest	1.0 (Ref.)	1.0 (Ref.)
West	0.99 (0.96, 1.03)	0.90 (0.83, 0.99)
Northeast	0.98 (0.95, 1.01)	0.99 (0.92, 1.07)
South	1.06 (1.03, 1.09)	1.29 (1.22, 1.37)
Puerto Rico	1.30 (1.13, 1.49)	3.25 (2.66, 3.97)
<b>Race</b>		
Other	1.0 (Ref.)	1.0 (Ref.)
Black	1.05 (1.00, 1.11)	1.60 (1.44, 1.79)
White	1.24 (1.18, 1.30)	0.97 (0.88, 1.08)
<b>Reduced multivariate model</b>		
<b>Age, y</b>		
<50	1.0 (Ref.)	‡
50 to 59	1.37 (1.26, 1.49)	
60 to 69	1.57 (1.45, 1.70)	
70 to 79	2.04 (1.89, 2.20)	
80 to 89	3.13 (2.90, 3.38)	
≥90	5.13 (4.73, 5.57)	

Continued

**Table 2.** Continued

Characteristic	Mortality	Major Amputation
<b>Clinical presentation</b>		
Rest pain	1.0 (Ref.)	1.0 (Ref.)
Ulcer	1.56 (1.52, 1.60)	1.41 (1.32, 1.52)
Gangrene	2.35 (2.28, 2.41)	5.60 (5.24, 5.97)
Chronic kidney disease	1.82 (1.79, 1.86)	‡

\*Values are hazard ratio (95% confidence interval).

†Variable not retained in multivariate model.

‡Variable not retained in reduced multivariate model.

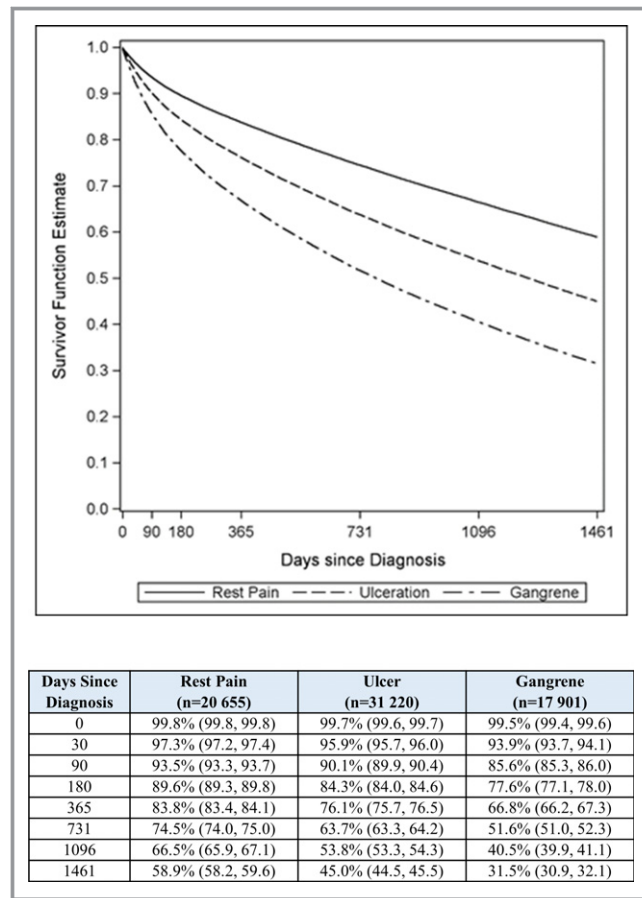
amputation, statistically significant associations were observed with mortality among all 13 baseline variables and with major amputation among 9 of 13 baseline variables. In a reduced multivariate model, older age (hazard ratio, 5.1 for age ≥90 versus <50 years), greater clinical presentation severity (hazard ratio, 2.4 for gangrene, 1.6 for ulcer versus rest pain), and chronic kidney disease (hazard ratio, 1.8) had the strongest associations with mortality risk. Greater clinical presentation severity (hazard ratio, 5.6 for gangrene, 1.4 for ulcer versus rest pain) was the only significant predictor of major amputation in the reduced model; patient race was not a significant explanatory variable in the final model (Table 2).

Patient survival and freedom from major amputation through 4 years were lower in patients with gangrene (Figures 1 and 2). Among patients who underwent a major treatment, 4-year survival was 45% for endovascular revascularization, 51% for surgical revascularization, and 21% for major amputation (all pair-wise comparisons statistically significant at  $P<0.001$ ; Figure S3). Patients undergoing primary major amputation had the worst prognosis across each clinical presentation category, with 4-year survival of 34% in those with rest pain, 22% in those with ulcer, and 20% in those with gangrene (Figure S4). Major amputation rates in follow-up were 3.9% for endovascular revascularization, 6.0% for surgical revascularization, and 11.0% for primary major amputation ( $P<0.001$  for each revascularization procedure versus major amputation). Comparing patients of black, other, and white races, black patients had the highest major amputation rates in each clinical presentation category. Corresponding major amputation rates were 10.3%, 6.0%, and 5.4% in patients presenting with rest pain, 15.5%, 9.5%, and 8.9% in patients presenting with ulcer, and 35.5%, 22.6%, and 24.8% in patients presenting with gangrene ( $P<0.001$  for black versus each race among each clinical presentation category).

### Healthcare Costs

Complete cost data were available in 70 160 (97%) patients in which Medicare was the primary payer. During the 12 months





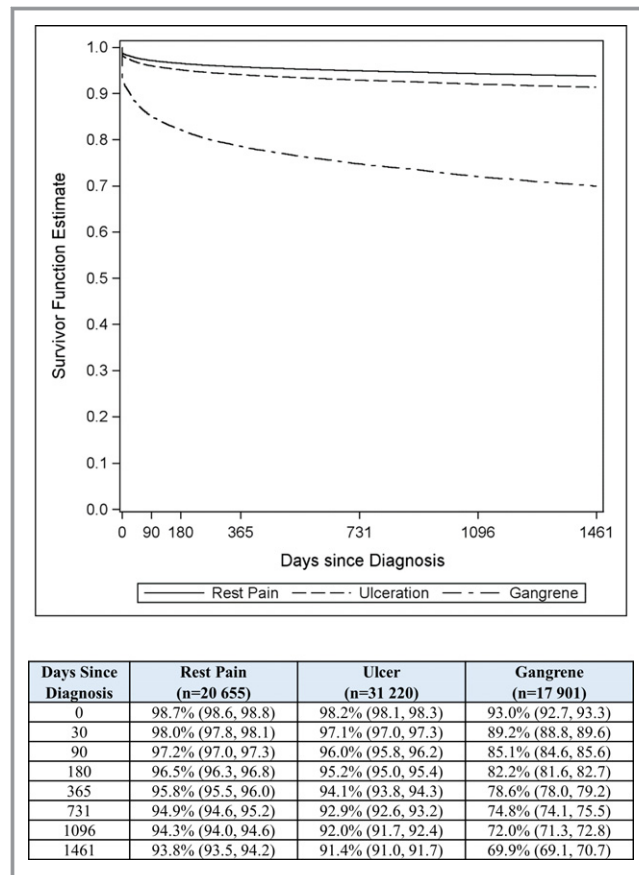
**Figure 1.** Patient survival over 4 years following diagnosis of critical limb ischemia by clinical presentation in entire sample. \* $P < 0.001$  vs ulcer; † $P < 0.001$  vs gangrene; ‡ $P < 0.001$  vs rest pain.

before CLI diagnosis, average cost was \$25 100 per patient. Average cost per patient over the follow-up period was \$93 800, of which 62% was attributable to hospital inpatient costs, 20% to hospital outpatient costs, and 18% to physician/supplier costs. Average per-patient costs during follow-up based on initial clinical presentation were \$78 300 for rest pain, \$91 200 for ulcer, and \$116 400 for gangrene (all pair-wise comparisons statistically significant at  $P < 0.001$ ). When adjusting for follow-up duration, cost per patient-year after CLI diagnosis was \$35 700. Among the entire sample, total healthcare costs were \$6.5 billion over the study period.

### Propensity-Matched Comparison of Primary Endovascular Revascularization, Surgical Revascularization, and Major Amputation

After propensity-score matching, 9942 patients were available for comparison of primary endovascular revascularization, surgical revascularization, or major amputation (3314 per group). Propensity-score matching resulted in comparable baseline characteristics among these groups. The propensity-matched sample presented with greater clinical presentation

severity than in the unmatched sample (66% versus 25% with gangrene; Table S2), which was attributable to the overlap in propensity score distribution among the 3 groups that allowed a 1:1:1 match in most patients treated with primary major amputation. The 4-year survival estimates were 38% with endovascular revascularization (median survival, 2.7 years), 40% with surgical revascularization (median survival, 2.9 years), and 23% with major amputation (median survival, 1.3 years). Survival was higher when comparing each revascularization approach to major amputation ( $P < 0.001$ ), but was not different comparing endovascular to surgical revascularization. The higher relative mortality risk associated with major amputation versus revascularization was mainly observed in the first 6 months, after which the mortality rate was comparable (Figure 3). Patients undergoing primary major amputation had the worst prognosis, regardless of clinical presentation severity, with 4-year survival estimates of 34% in those with rest pain, 21% in those with ulcer, and 22% in those with gangrene (Figure 4). Major amputation rates in follow-up were 6.5% for endovascular revascularization, 9.6% for surgical revascularization, and 10.6% for primary major amputation ( $P < 0.001$  for all pair-wise comparisons).



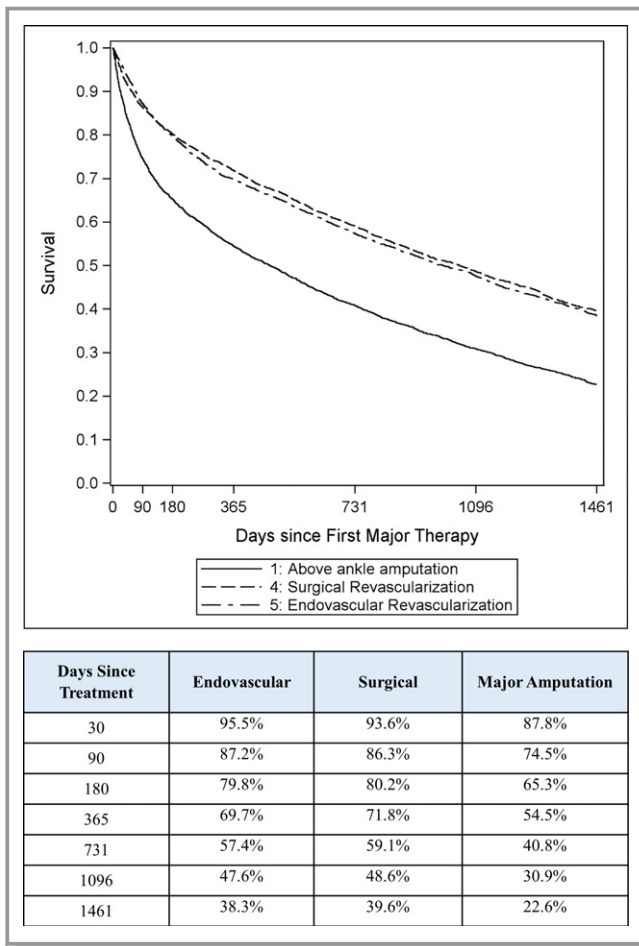
**Figure 2.** Freedom from major amputation over 4 years following diagnosis of critical limb ischemia by clinical presentation in entire sample. \* $P < 0.001$  vs ulcer; † $P < 0.001$  vs gangrene; ‡ $P < 0.001$  vs rest pain.

Complete cost data in which Medicare was primary payer were available in 9219 (93%) of matched patients. During the 12 months before CLI diagnosis, the average cost was \$27 500 in patients ultimately treated with endovascular revascularization, \$26 100 in those treated with surgical revascularization, and \$38 300 in those treated with major amputation ( $P < 0.001$  comparing each revascularization approach to major amputation). Average cost per patient over the follow-up period was \$117 800, of which 68% was attributable to hospital inpatient costs, 14% to hospital outpatient costs, and 17% to physician/supplier costs. Average cost per patient over the follow-up period according to initial major treatment was \$121 900 for endovascular revascularization, \$122 700 for surgical revascularization, and \$107 500 for major amputation ( $P < 0.001$  comparing each revascularization approach with major amputation). The lower cost associated with major amputation was attributed to lower survival rates. When adjusting for follow-up duration, cost per patient-year was \$49 700 for endovascular revascularization, \$49 200 for surgical revascularization, and \$55 700 for major amputation ( $P < 0.001$  comparing each revascularization approach to major amputation).

## Discussion

Results of this claims analysis of the US Medicare population highlight the considerable clinical burden and high cost in patients following an initial diagnosis with CLI. Long-term survival and cost are comparable between revascularization techniques, with lower major amputation rates following endovascular revascularization. Primary major amputation portends a poor prognosis even when adjusting for demographics, medical history, and disease severity. Compared with revascularization, primary major amputation is associated with shorter survival time, increased risk of second major amputation, and higher healthcare costs. These results were generally consistent regardless of patient characteristics and clinical presentation.

This study showed that among incident cases of CLI, 29% will die or undergo major amputation in the first year. Furthermore, the typical patient will endure multiple revascularization procedures over a median survival of only 3.5 years. For comparison, the estimated additional life expectancy among age- and sex-matched adults is 13.4 years.<sup>16</sup> Survival following CLI diagnosis is lower than that of heart failure,<sup>17</sup> stroke,<sup>18</sup> and most cancers.<sup>19</sup> Given that CLI is



**Figure 3.** Patient survival over 4 years following first major therapy for critical limb ischemia in matched patients. \* $P < 0.001$  vs major amputation.

underdiagnosed, increasing in prevalence, and responsible for significant risk to life and limb, considerable efforts are needed to raise disease awareness, refine diagnostic algorithms, and establish evidence-based treatment pathways. Assuming an annual CLI incidence of 0.26%, 49.2 million adults aged  $\geq 65$  years in the United States in 2016, and estimated 4-year costs of \$93 800, this yields  $\approx$ \$12 billion in annual costs attributable to incident cases of CLI.

Consensus recommendations cite revascularization as the optimal treatment for patients with CLI<sup>20</sup> given the poor prognosis<sup>21</sup> and functional impairment<sup>22</sup> following major amputation. Allie et al<sup>23</sup> reported that 51% of CLI patients had no diagnostic vascular evaluation preceding primary amputation. Goodney et al<sup>10</sup> reported that 54% of patients with CLI had no vascular procedures in the year before undergoing amputation. In the current study, 51% of patients undergoing primary major amputation received no previous revascularization. These data highlight the heterogenous approach to CLI management and suggest that many patients

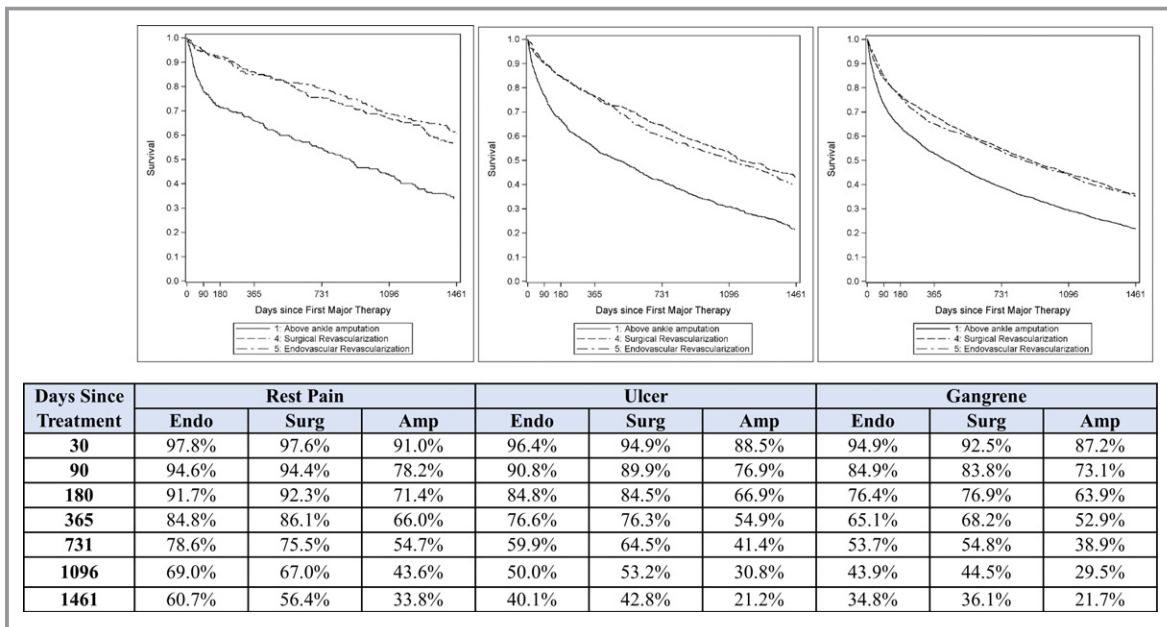
may not undergo adequate diagnostic evaluation with imaging at initial presentation, potentially leading to unnecessary amputations and associated morbidity. On balance, primary major amputation may be appropriate in select patients, such as nonambulatory nursing home residents, where there is little chance of improved function or survival with revascularization.<sup>7</sup> We noted important racial differences in major amputation rates in this study. Frequency of primary major amputation and subsequent major amputations was disproportionately higher in patients of black race versus white and other races that were not fully explained by differences in patient characteristics. Additional study is warranted to elucidate the factors that result in the striking racial disparities observed in clinical presentation and CLI management strategies.

Because most patients with CLI are elderly with multiple comorbidities, endovascular techniques have been adopted with increasing frequency.<sup>24</sup> Although primary revascularization was superior to major amputation in every scenario in this study, whether an endovascular first strategy in CLI management improves long-term patient outcomes remains unclear. In the current study, long-term survival was comparable between revascularization approaches whereas major amputation risk was lower with endovascular revascularization. A large ongoing National Institutes of Health-sponsored multicenter, randomized controlled trial of endovascular versus surgical therapy in 2100 CLI patients was designed to address this question with greater rigor.<sup>25</sup> Regardless of revascularization approach, an interdisciplinary care team skilled in wound healing, foot surgery, medical evaluation, and medical care should assist with patient care given the systemic involvement of the disease process.<sup>20,26</sup>

Effective October 1, 2015, *ICD-10-CM* replaced *ICD-9-CM* for coding purposes in the United States. The new coding system offers greater detail and specificity for the purposes of diagnosing patients afflicted with CLI. The *ICD-10-CM* offers dozens of codes describing laterality, location of wounds, and disease burden. This CLI patient analysis would be more intensive using *ICD-10-CM* methodology and would lend itself to subset analyses at a greater investment of time and labor. This raises the question of whether this specific disease would be best served by the assignment of a Medicare Severity Diagnosis Related Group (MS-DRG) code to facilitate the monitoring of this population moving forward. Such a code would allow for hospitals as well as public and private payers to prospectively track the incidence and burden of this population and make strategic investments to offset the effects of this disease.

Strengths of this research include long-term follow-up in a nation-wide sample of patients initially diagnosed with CLI and managed under real-world conditions. Furthermore, the comparison of 3 primary CLI treatment strategies in unmatched and matched samples is novel. There were also





**Figure 4.** Patient survival over 4 years following first major therapy for critical limb ischemia by clinical presentation (A, rest pain; B, ulcer; C, gangrene) in matched patients. Amp indicates major amputation; endo, endovascular; surg, surgical. \* $P < 0.001$  vs major amputation within each clinical presentation category.

several limitations of this study inherent to administrative claims analysis that warrant further discussion. First, as a retrospective evaluation of claims records, potential exists for misclassification of important demographic, medical history, diagnostic, or procedural data. Second, CLI diagnosis in this study required a primary *ICD-9-CM* code of 440.22, 440.23, or 440.24. Other codes such as 707.14 (ulcer of heel and midfoot) or 785.4 (gangrene), with or without associated procedure codes, could have justifiably been used. However, the addition of procedure codes has been shown to reduce sensitivity and overall agreement when applied to well-qualified CLI patients.<sup>27</sup> Because there are no universally accepted *ICD-9-CM* codes to identify CLI and that the focus of this study was not to determine CLI incidence, but to characterize clinical outcome following diagnosis, a focused list of *ICD-9-CM* codes for CLI diagnosis was used to limit bias introduced by inclusion of cases with unrelated conditions. Third, we were unable to control for laterality where repeat procedures may have been performed on the contralateral leg. Fourth, the rationale for treatment decisions cannot be determined from this research. For example, although primary major amputation was performed in 6% of patients, whether amputation was performed because of standard institutional practice, extensive gangrene, inability to ambulate, or otherwise is unknown. Finally, despite the use of propensity-score matching to adjust for selection bias among major treatments, the possibility that unmeasured patient characteristics were different among treatment groups and may have influenced outcomes cannot be discounted. For example, in

the propensity-matched sample, characteristics of patients initially treated with major amputation were comparable to those treated with revascularization; yet, healthcare costs in the year before CLI diagnosis were higher in those with major amputation as primary treatment. This suggests that patients initially managed with major amputation may have presented with greater unmeasured comorbidity that negatively influenced subsequent clinical outcomes. Finally, owing to the greater clinical severity in patients treated with primary major amputation, the propensity-matched sample presented with gangrene more frequently than in unmatched cases. Still, the observation that primary major amputation resulted in the lowest survival rates in patients with rest pain, ulcer, and gangrene demonstrates the utility of the propensity-matched results.

### Conclusions

Patients initially diagnosed with CLI suffer poor long-term prognosis and generate high healthcare costs. Long-term survival and cost are comparable between revascularization techniques, with lower major amputation rates following endovascular revascularization. Compared with each revascularization approach, primary major amputation is associated with shorter survival time, higher risk of subsequent major amputation, and higher healthcare costs. Results from this observational research may be susceptible to bias attributable to the influence of unmeasured confounders. Considerable efforts are needed to raise disease awareness, implement

coding to better define and identify the disease, refine diagnostic algorithms, establish evidence-based treatment pathways, and address the high mortality rates associated with this diagnosis.

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Mustapha reports consultancy with Abbott Vascular, Bard Peripheral Vascular, Boston Scientific, Cardiovascular Systems, Cook Medical, Medtronic, Spectranetics, and Terumo. Katzen is a member of the Scientific Advisory Board of Boston Scientific, WL Gore, and Philips Healthcare. Neville is a member of the Scientific Advisory Board of WL Gore, Cormatrix, Graftworx, and Tissue Analytics; holds equity investment in Graftworx and Tissue Analytics; and received research grants from WL Gore and Medtronic. Lookstein reports consultancy with Boston Scientific and Medtronic; and is a member of the Scientific Advisory Board of Boston Scientific and Medtronic. Zeller received honoraria for speaking or moderating educational programs from 480 biomedical, Abbott Vascular, Biotronik, Boston Scientific Corp., Cordis, Medtronic, Shockwave Medical, Spectranetics, Veryan/Novate, Phillips-Volcano, and WL Gore; reports consultancy with Boston Scientific Corp., Medtronic, Gore & Associates, Spectranetics, and Veryan/Novate; and holds equity investment in QT Medical and Veryan/Novate. Miller reports consultancy with CLI Global Society, Spectranetics, and TriReme Medical. Jaff is a noncompensated advisor to Abbott Vascular, Boston Scientific, Cordis, and Medtronic Vascular; reports consultancy with Micell, Philips/Volcano, Venarum, American Orthotics and Prosthetics Association, and Vactronix; holds equity investment in PQ Bypass, Vascular Therapies, Primacea, and Embolitech; and is a board member of Greenway Health.

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# **SUPPLEMENTAL MATERIAL**

**Table S1. Coding scheme to identify interventional procedures in Medicare eligible patients diagnosed with critical limb ischemia in 2011.**

<b>Therapy Code</b>	<b>Description</b>
<b>Endovascular Revascularization *</b>	
<i>ICD-9-CM Code</i>	
00.55	Insertion of drug eluting peripheral vessel stent
00.60	Insertion of drug-eluting stent(s) of superficial femoral artery
39.50	Angioplasty or atherectomy of non-coronary vessel
39.90	Insertion of non-drug-eluting, non-coronary artery stent
<i>CPT Code</i>	
37220	Iliac revasc
37221	Iliac revasc w/stent
37222	Iliac revasc add-on
37223	Iliac revasc w/stent add-on
37224	Fem/popl revas w/tla
37225	Fem/popl revas w/ather
37226	Fem/popl revasc w/stent
37227	Fem/popl revasc stnt & ather
37228	Tib/per revasc w/tla
37229	Tib/per revasc w/ather
37230	Tib/per revasc w/stent
37231	Tib/per revasc stent & ather
37232	Tib/per revasc add-on
37233	Tibper revasc w/ather add-on
37234	Revasc opn/prq tib/pero stent
37235	Tib/per revasc stnt & ather
37236	Open/perq place stent 1st
37237	Open/perq place stent ea add
37238	Open/perq place stent same
37239	Open/perq place stent ea add
<b>Surgical Revascularization *</b>	
<i>ICD-9-CM Code</i>	
38.08	Incision of lower limb arteries
38.16	Endarterectomy of abdominal arteries
38.18	Endarterectomy of lower limb arteries
38.38	Resection of vessel with anastomosis
38.40	Resection of vessel with replacement, unspecified site
38.48	Resection of vessel with replacement, lower limb arteries
38.49	Resection of vessel with replacement, lower limb veins
38.68	Other excision of vessel
38.88	Other surgical occlusion of vessels
39.25	Aorta-iliac-femoral bypass
39.29	Other (peripheral) vascular shunt or bypass



39.49	Other revision of vascular procedure
<i>CPT Code</i>	
35302	Rechanneling of artery
35303	Rechanneling of artery
35304	Rechanneling of artery
35305	Rechanneling of artery
35306	Rechanneling of artery
35331	Rechanneling of artery
35351	Rechanneling of artery
35355	Rechanneling of artery
35361	Rechanneling of artery
35363	Rechanneling of artery
35371	Rechanneling of artery
35372	Rechanneling of artery
35452	Repair arterial blockage
35472	Repair arterial blockage
35500	Harvest vein for bypass
35521	Art byp grft axill-femoral
35533	Art byp grft axill/fem/fem
35556	Art byp grft fem-popliteal
35558	Art byp grft fem-femoral
35563	Art byp grft ilioiliac
35565	Art byp grft iliofemoral
35566	Art byp fem-ant-post tib/prl
35571	Art byp pop-tibl-prl-other
35583	Vein byp grft fem-popliteal
35585	Vein byp fem-tibial peroneal
35587	Vein byp pop-tibl peroneal
35621	Art byp axillary-femoral
35623	Art byp axillary-pop-tibial
35654	Art byp axill-fem-femoral
35656	Art byp femoral-popliteal
35661	Art byp femoral-femoral
35663	Art byp ilioiliac
35665	Art byp iliofemoral
35666	Art byp fem-ant-post tib/prl
35671	Art byp pop-tibl-prl-other
35681	Composite byp grft pros&vein
35682	Composite byp grft 2 veins
35683	Composite byp grft 3/> segmt
35686	Bypass graft/av fist patency
35700	Reoperation bypass graft
35875	Removal of clot in graft
35876	Removal of clot in graft
35879	Revise graft w/vein

35881	Revise graft w/vein
35883	Revise graft w/nonauto graft
35884	Revise graft w/vein
35903	Excision graft extremity
<b>Amputation above the ankle</b>	
<i>ICD-9-CM Code</i>	
84.10	Lower limb amputation (NOS)
84.16	Disarticulation of knee
84.17	Amputation above knee
84.18	Disarticulation of hip
84.19	Abdominopelvic amputation
<i>CPT Code</i>	
27290	Amputation of leg at hip
27295	Amputation of leg at hip
27590	Amputate leg at thigh
27591	Amputate leg at thigh
27592	Amputate leg at thigh
27594	Amputation follow-up surgery
27596	Amputation follow-up surgery
27598	Amputate lower leg at knee
27880	Amputation of lower leg
27881	Amputation of lower leg
27882	Amputation of lower leg
27884	Amputation follow-up surgery
27886	Amputation follow-up surgery
<b>Amputation below the ankle</b>	
<i>ICD-9-CM Code</i>	
84.11	Amputation of toe
84.12	Amputation through foot
84.13	Disarticulation of ankle
84.14	Amputation of ankle through malleoli of tibia and fibula
84.15	Other amputation below knee
<i>CPT Code</i>	
27888	Amputation of foot at ankle
27889	Amputation of foot at ankle
28130	Removal of ankle bone
28140	Removal of metatarsal
28800	Amputation of midfoot
28805	Amputation thru metatarsal
28810	Amputation toe & metatarsal
28820	Amputation of toe
28825	Partial amputation of toe
28124	Partial removal of toe
28126	Partial removal of toe
28150	Removal of toe

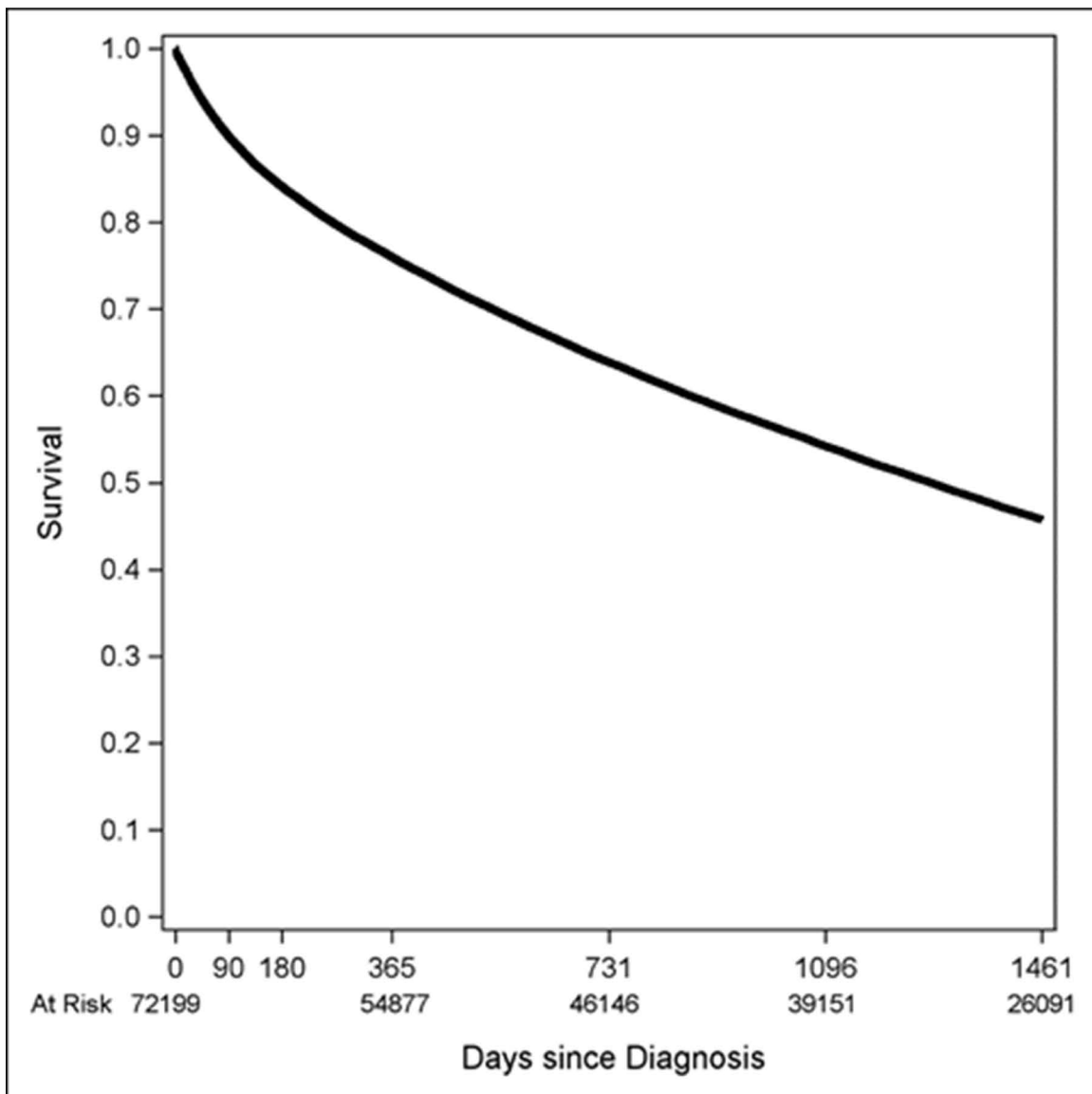
28153	Partial removal of toe
28160	Partial removal of toe

CPT indicates Current Procedural Terminology; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

\*CPT codes 35221, 35226, 35256, and 35286 (repair blood vessel lesion with or without patch angioplasty) were included in revascularization analyses, but was not included in endovascular or surgical revascularization analyses due to uncertainty in definition.

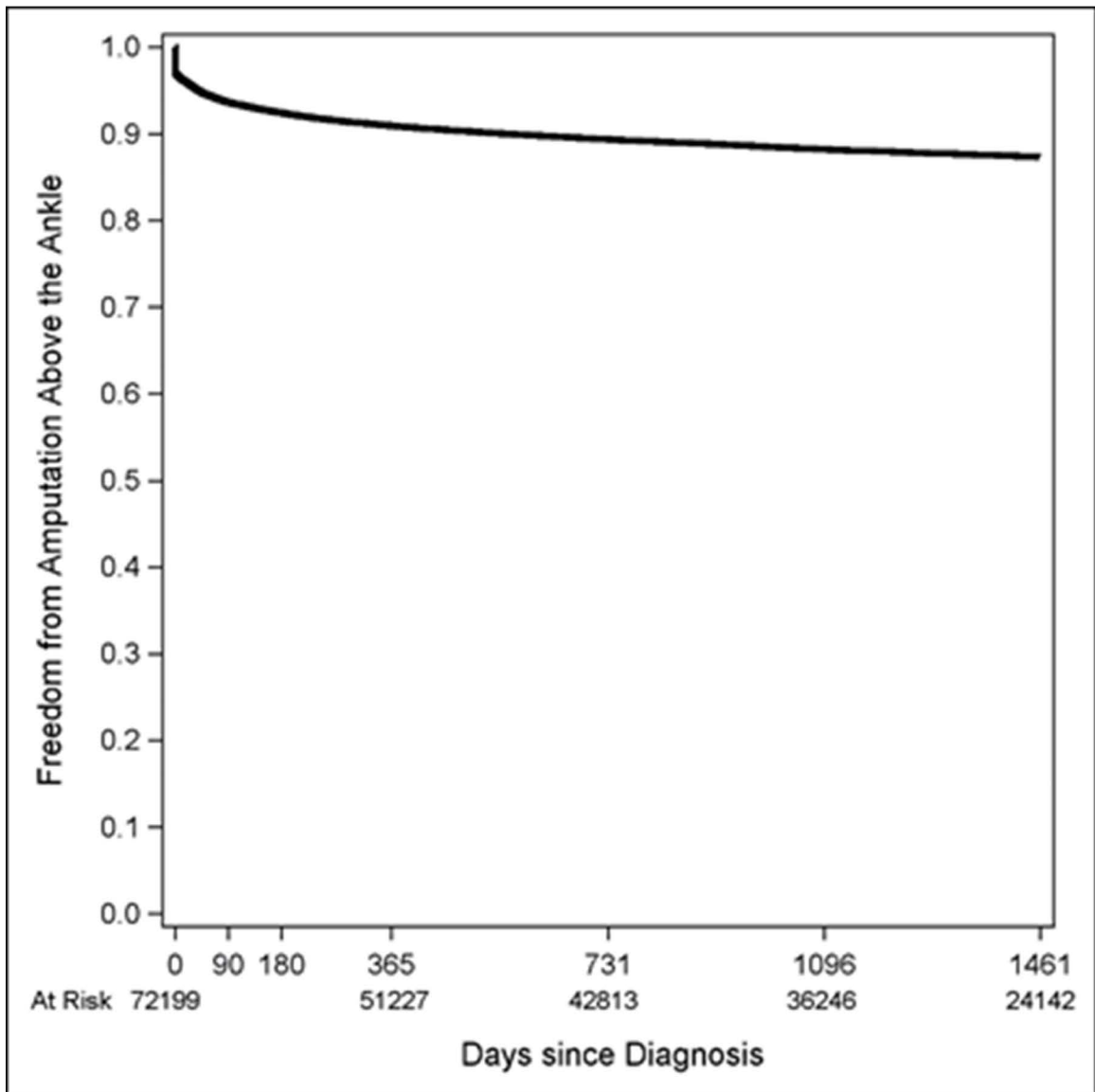
**Table S2. Baseline characteristics of Medicare eligible patients diagnosed with critical limb ischemia in 2011 categorized by first major therapy in propensity-matched sample.**

Characteristic	Unmatched Sample				Matched Sample			
	Endovascular	Surgical	Major Amputation	P-value	Endovascular	Surgical	Major Amputation	P-value
No. of patients	28 530	14 283	3982		3314	3314	3314	
<i>Geography</i>								
Region				<0.001				0.17
South	12 250 (44)	5713 (41)	2057 (53)		1666 (50)	1650 (50)	1660 (50)	
Midwest	7177 (26)	3390 (24)	703 (18)		644 (19)	704 (21)	660 (20)	
Northeast	4756 (17)	3037 (22)	653 (17)		638 (19)	576 (17)	624 (19)	
West	3795 (14)	1916 (14)	365 (9)		338 (10)	352 (11)	353 (11)	
Puerto Rico	93 (<1)	39 (<1)	90 (2)		28 (<1)	32 (<1)	17 (<1)	
Population density				<0.001				<0.01
Urban	25 339 (90)	12 715 (90)	3345 (86)		2994 (90)	2928 (88)	2921 (88)	
Rural	2732 (10)	1380 (10)	523 (14)		320 (10)	386 (12)	393 (12)	
<i>Demographics</i>								
Male sex	14 773 (52)	8281 (58)	2107 (53)	<0.001	1875 (57)	1891 (57)	1852 (56)	0.62
Age, yr	74±11	72±11	76±12	<0.001	74±11	74±10	74±12	0.95
Race				<0.001				0.21
White	21 374 (75)	11 290 (79)	2426 (61)		2253 (68)	2210 (67)	2220 (67)	
Black	5346 (19)	2352 (17)	1340 (34)		921 (28)	923 (28)	927 (28)	
Other/unknown	1723 (6)	599 (4)	209 (5)		140 (4)	181 (5)	167 (5)	
<i>Medical history</i>								
Hypertension	21 205 (74)	10 333 (72)	2937 (74)	<0.001	2451 (74)	2421 (73)	2421 (73)	0.63
Diabetes	16 776 (59)	6798 (48)	2268 (57)	<0.001	1870 (56)	1870 (56)	1889 (57)	0.86
Coronary artery disease	14 440 (51)	7027 (49)	1854 (47)	<0.001	1535 (46)	1593 (48)	1597 (48)	0.23
Chronic kidney disease	10 162 (36)	3853 (27)	1507 (38)	<0.001	1179 (36)	1158 (35)	1212 (37)	0.38
Hyperlipidemia	7775 (27)	4059 (28)	808 (20)	<0.001	682 (21)	747 (23)	723 (22)	0.15
Smoking	5754 (20)	4180 (29)	777 (20)	<0.001	642 (19)	700 (21)	721 (22)	<0.05
<i>Clinical presentation</i>								
Rest pain	8365 (29)	5977 (42)	276 (7)	<0.001	279 (8)	288 (9)	267 (8)	0.93
Ulcer	13 625 (48)	4786 (34)	906 (23)		846 (26)	841 (25)	851 (26)	
Gangrene	6540 (23)	3520 (25)	2800 (70)		2189 (66)	2185 (66)	2196 (66)	

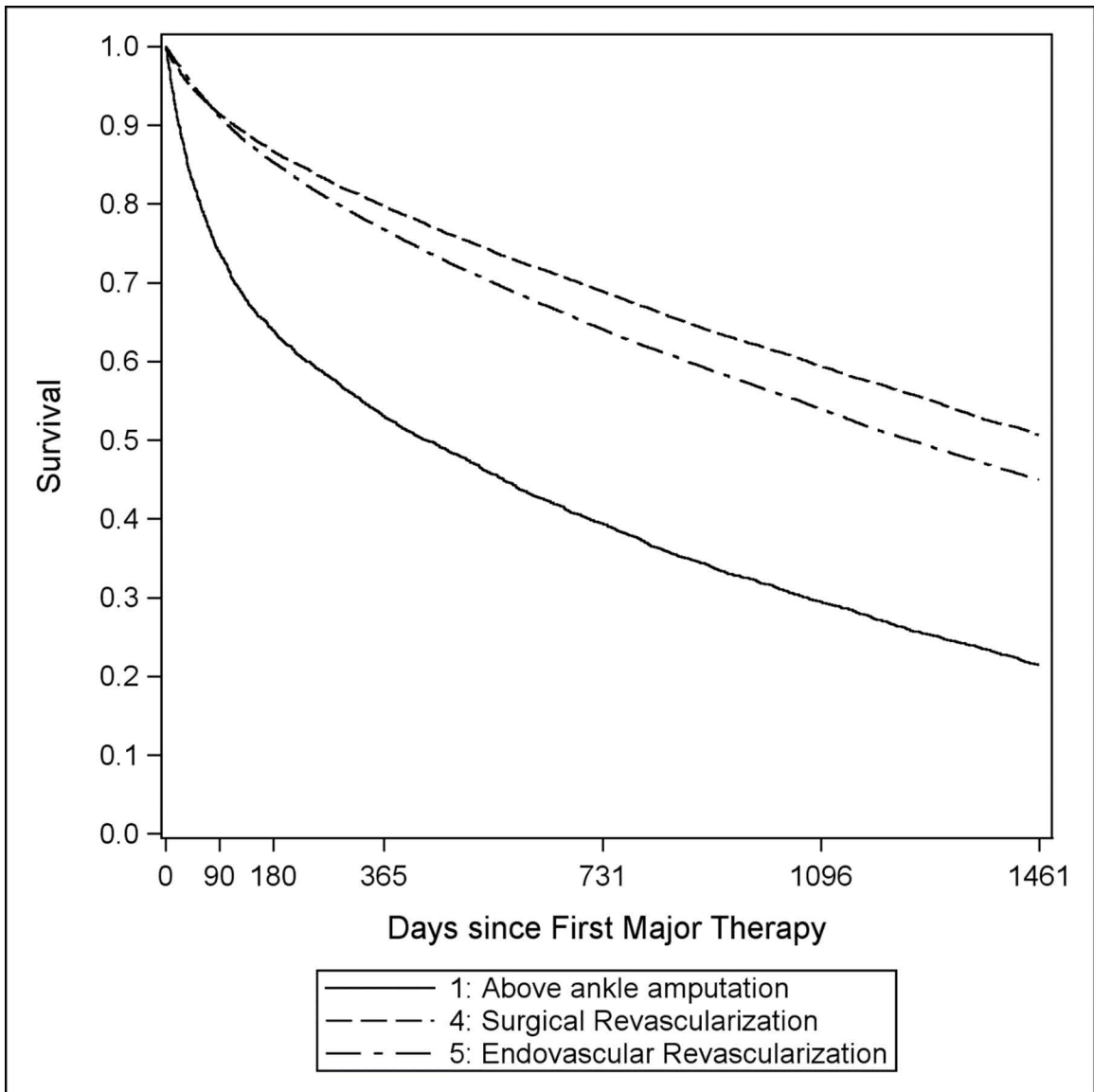


Days Since Diagnosis	Survival (95% CI)	Cumulative Number of Deaths	Number of Patients Remaining at Risk
0	99.7% (99.6, 99.7)	251	72199
30	95.7% (95.6, 95.9)	3088	69201
90	89.9% (89.6, 90.1)	7322	64925
180	84.1% (83.8, 84.3)	11511	60736
365	76.0% (75.6, 76.3)	17357	54877
731	63.9% (63.5, 64.2)	26077	46146
1096	54.2% (53.8, 54.6)	33062	39151
1461	45.7% (45.4, 46.1)	39024	26091

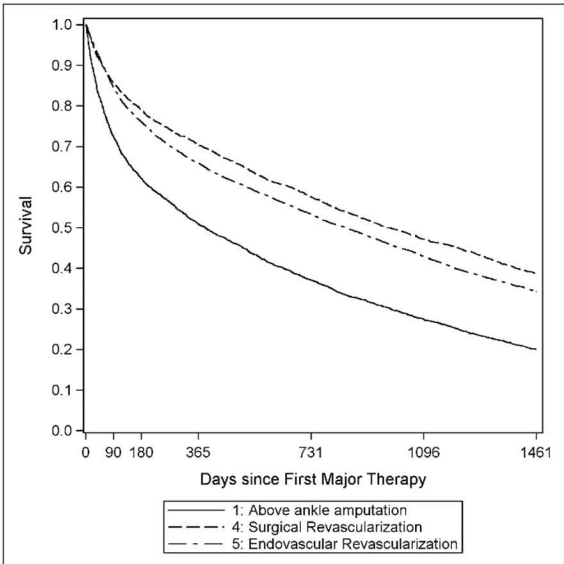
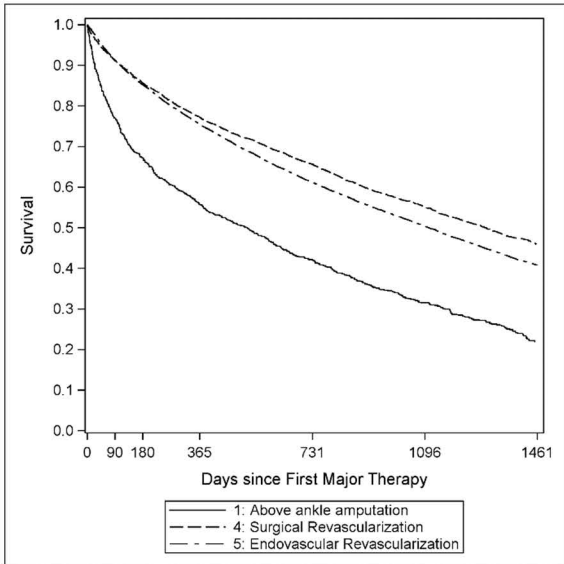
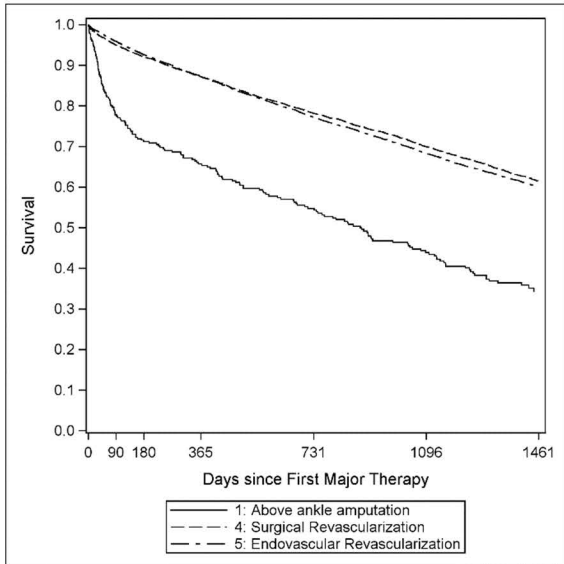




Days Since Diagnosis	Freedom from Amputation (95% CI)	Cumulative Number of Patients with Amputations	Number of Patients Remaining at Risk
0	97.0% (96.8, 97.1)	2185	72199
30	95.4% (95.2, 95.5)	3317	66277
90	93.7% (93.5, 93.8)	4479	61458
180	92.4% (92.2, 92.6)	5256	57128
365	90.9% (90.7, 91.2)	6139	51227
731	89.4% (89.1, 89.6)	6958	42813
1096	88.2% (88.0, 88.5)	7471	36246
1461	87.3% (87.1, 87.6)	7795	24142



Days Since Treatment	Endovascular	Surgical	Major Amputation
30	96.7%	96.0%	87.4%
90	91.1%	91.4%	73.7%
180	85.3%	86.7%	63.9%
365	76.8%	79.7%	53.0%
731	64.1%	68.9%	39.4%
1096	53.9%	59.4%	29.5%
1461	45.0%	50.6%	21.4%



Days Since Treatment	Rest Pain			Ulcer			Gangrene		
	Endo	Surg	Amp	Endo	Surg	Amp	Endo	Surg	Amp
30	98.4%	97.7%	90.2%	96.9%	96.0%	88.5%	94.2%	93.4%	86.7%
90	95.9%	95.0%	77.8%	91.3%	91.1%	76.9%	84.6%	85.6%	72.3%
180	92.6%	92.0%	71.2%	85.2%	85.7%	67.2%	76.1%	79.0%	62.1%
365	87.3%	87.2%	65.7%	75.5%	77.2%	55.8%	65.9%	70.4%	50.9%
731	77.2%	78.2%	54.8%	61.2%	65.6%	42.0%	53.3%	57.6%	37.0%
1096	68.3%	70.0%	43.9%	50.4%	55.1%	31.5%	42.9%	47.2%	27.5%
1461	60.2%	61.4%	34.2%	40.8%	45.9%	21.7%	34.2%	38.7%	20.0%