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The problem of critical limb ischemia

Peripheral arterial disease refers to the problem of impaired arterial circulation to the lower extremities (specifically, an ankle-brachial index of <0.90), most often due to atherosclerosis. Less severe peripheral arterial disease may initially be asymptomatic (classified as Rutherford category 0 peripheral arterial disease) or may be manifest as mild, moderate, or severe claudication (Rutherford categories 1 to 3, respectively). As the degree of tissue perfusion becomes more impaired, peripheral arterial disease may lead to ischemic rest pain (Rutherford category 4); tissue loss in the setting of a salvageable foot, manifesting as ischemic foot ulcers, toe gangrene, or nonhealing wounds (Rutherford category 5); or severe foot necrosis extensive enough to preclude foot salvage and instead requiring major amputation (Rutherford category 6). The term critical limb ischemia (CLI) refers to the presence of either rest pain or tissue loss (Rutherford categories 4 to 6) for more than 2 weeks, with arterial insufficiency corroborated by objective testing (specifically, ankle pressure <50 mmHg and/or toe pressure <30 mmHg). Patients with intact sensation often present with claudication; patients with impaired foot sensation and/or proprioception (commonly diabetic patients with peripheral neuropathy) often do not notice symptoms of claudication or rest pain. Instead, the first manifestation of peripheral arterial disease in these patients is typically tissue loss in the form of a nonhealing ulcer.

Without revascularization to improve the arterial circulation and increase tissue perfusion, patients with Rutherford category 5 CLI are at high risk of limb loss. Efforts to avoid limb loss are typically quite challenging for physicians because intervention is laborious (often requiring complex surgical revascularizations followed by repeated soft tissue debridements, minor amputations, and/or skin grafting), costly (estimated to be on the order of $3 billion for US diabetic patients alone), and may still result in limb loss in spite of a successful revascularization.

The burden of CLI and amputations in the United States

Peripheral arterial disease is common, affecting approximately 5 million persons in the United States alone. Non-Hispanic blacks, people with diabetes, and the elderly (persons over 70 years old) appear disproportionately affected, with prevalence rates of 7.9%, 10.8%, and 14.5% in these 3 groups, respectively. It is estimated that approximately 300,000 patients in the United States will present with CLI in a given year. In 2006, 66,000 people with diabetes underwent nontraumatic lower extremity amputation; with a mean hospital charge of $56,400, this would account for $3.7 billion for amputations alone.

Two demographic features suggest that the prevalence of CLI will increase significantly over the course of the next 20 years. First, the number of patients aged 65 or older is predicted to increase from 46 million (13.0% of the population) currently to approximately 80 million (19.8% of the population) in 2030 and 103 million (21.1%) in 2050. Given that the prevalence of peripheral arterial disease increases dramatically with age (from 1.9% among men aged 50 to 59 to 6.7% among men aged 60 to 69, and 13.7% among men 70 and older), aging alone may account for a 50% increase in the number of US persons presenting with CLI over the next 2 decades. Second, diabetes will continue to have a major impact on the burden of CLI in the United States. The incidence of diabetes in this country has risen dramatically, from an age-adjusted rate of 2.9% in 1990 to 5.7% in 2007 (approximately 17.4 million persons in the US), and this may increase further, to 8.3%, by 2030; with projected population growth, this will represent approximately 29.8 million persons. Further compounding the problem is the prediction that a larger proportion of this future US diabetic population is expected to be elderly. Among patients with peripheral arterial disease and diabetes, the annual incidence of foot ulcers reaches 13.8% and the risk of major amputation reaches 3.7% per year.

Foot care (including inpatient and outpatient wound care, treatment of infections, and ampu-
tations) is expensive and represents the second highest cost driver among diabetic patients after dialysis. Finally, major amputation has the biggest negative impact on quality of life among diabetic patients than any other complication. Given these facts, it should be clear that the predicted rise in the number of diabetic patients in the US will be an important financial burden on our health care system and greatly affects the health and quality of life of the US population.

Cost-effectiveness, health care “value” and CLI
With US health care expenditures now exceeding $2 trillion (17% of the US gross national product), many are calling for health care costs to be considered when deciding on treatment options. Indeed, there are already indications that governmental and nongovernmental payers of US health care will take cost-effectiveness into consideration in coverage decisions. The foundation for the management of CLI is based on the outcome parameters of interest to vascular surgeons—namely, target vessel patency and only recently have patient-oriented outcomes such as quality of life and functional status. The objective is to provide the clinician and researcher interested in limb salvage a comprehensive description of the effectiveness of limb salvage efforts that might serve as a foundation for further cost-effectiveness analyses.

Local wound care without revascularization
The natural history of Rutherford category 5 CLI
In an ideal health care system, all patients with Rutherford category 5 CLI would be promptly referred to a multidisciplinary team of providers with a clinical expertise in the management of this problem. The reality of the current US health care system, however, is that there is inadequate access to a primary care provider or podiatrist who would recognize the problem. The choice of providers for subsequent referral is seemingly haphazard, and the referral is often delayed or nonexistent. There may be many reasons for a delay in failure to refer, including: (1) a failure to recognize ischemia as contributing to the existence or persistence of a foot wound; (2) the patient lacking access to a primary care provider or podiatrist who might identify the problem; (3) the primary care provider or podiatrist (or patient) lacking access to an appropriate specialist or team of specialists; (4) patient preference (ie, refusal of surgery and/or a wish to avoid or postpone amputation, even before full discussion of the risks and benefits with a surgeon); and (5) the perception that the patient is too ill or has too limited a lifespan to merit attempts at revascularization or even primary amputation. Because a significant proportion of patients with Rutherford 5 CLI experience delays in treatment or never receive any intervention, it is worth considering the costs and outcomes of local wound care alone. If for no other reason, the evaluation of conservative management (in the parlance of decision analysis or cost-effectiveness analyses, the “do nothing” or “wait-and-see” option) should be considered in a framework for the evaluation of value and cost-effectiveness to serve as a baseline against which other management strategies are evaluated. Additionally, giving consideration to the option of conservative management can evaluate this strategy as an option for selected patients or help identify the financial and clinical costs associated with delays in diagnosis and/or treatment.

Several studies provide data on the contemporary natural history of conservative management of Rutherford category 5 CLI. The study with the longest follow-up and most specific inclusion criteria is an observational study by Marston and colleagues. In this study, 86 patients with chronic ulcers and a toe pressure < 40 mmHg or an ankle pressure < 70 mmHg were deemed poor candidates for revascularization for a variety of reasons. Wound care was performed by vascular specialists and included contemporary adjuncts such as negative pressure therapy and topical...
growth factors. Although ulcer healing was noted in approximately 50%, the major amputation rate was 38.4% by 1 year after the initiation of wound care. The placebo arms of several clinical trials of various medical interventions for ischemic ulcers and other observational studies are consistent with these outcomes, ie, they demonstrate high rates of wound improvement or healing but equally high rates of recurrence and major amputation.

Local wound care costs and impact on quality of life

The presence of a foot ulcer consistently appears to have a significant negative impact on quality of life (Table 1). In a study of 310 Swedish diabetic patients, for example, average EuroQol (EQ-5D) scores were 0.44 for those with active ulcers compared with 0.60 for those with healed ulcers (and compared with 0.31 for those with a major amputation). Further demonstrating the dismal overall quality of life of conservative management in this situation is a recent publication demonstrating mean EQ-5D scores of 0.34 among patients with "no-option" CLI. Component scores for the EQ-5D demonstrate that CLI impairs mobility, prevents the performance of daily activities, and is associated with physical pain and depression and/or anxiety.

Foot ulcers and nonhealing foot wounds have a significant financial impact as well. The well-cited report by Ramsey and colleagues initially brought this high cost to the attention of many clinicians. In this study, the additional health care costs associated with a new diabetic foot totaled $49,477 (2009 USD) during the first 2 years after diagnosis. The authors did note that the cost of care for these patients was higher than that of other diabetic control patients even before diagnosis of an ulcer (possibly reflecting a higher prevalence of other diabetic complications in this patient population). If these data are used, the annual excess cost associated with care of a diabetic foot ulcer would be $21,029 (2009 USD), a figure comparable to the estimates of $18,971 by Stockl and colleagues based on a single US institution data and of $25,981 by Harrington and associates based on Medicare claims data.

Outcomes after infrainguinal bypass

Graft patency, limb salvage and mortality after infrainguinal bypass for CLI

For decades, infrainguinal bypass had been the only option for revascularization in patients with CLI. Today it still remains the favored option of many vascular interventionalists, based predominately on the clinical outcomes associated with it. The traditional endpoints used to measure the success of infrainguinal bypass have been primary and secondary graft patency rates, limb salvage rates, and mortality, and countless studies — predominately cohort studies or case-control series — have reported these measures. The highest quality estimates of contemporary outcomes using these measures come from a meta-analysis of the 838 patients in the control arms of the 3 randomized trials involving patients with CLI (the PREVENT III [Project or Ex-Vivo Vein Graft Engineering via Transfection III] trial,

<table>
<thead>
<tr>
<th>First author</th>
<th>Instrument</th>
<th>No ulcer</th>
<th>Active ulcer</th>
<th>Major amputation</th>
<th>Surgical bypass</th>
<th>Endovascular intervention</th>
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<tr>
<td>Forbes</td>
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<td>0.62</td>
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<tr>
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<td>EQ-5D</td>
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<td>0.51 (men)</td>
<td></td>
<td>0.55 (women)</td>
<td></td>
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<tr>
<td>Davies</td>
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<td></td>
<td>0.43 (women)</td>
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<tr>
<td>Chetter</td>
<td>EQ-5D</td>
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<td></td>
<td>0.62</td>
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<tr>
<td>Ragnarson</td>
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<td></td>
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<td></td>
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<tr>
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<td>Van Hattum</td>
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<td>0.72</td>
<td>0.42</td>
<td>0.54</td>
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<tr>
<td>Weighted mean values</td>
<td>EQ-5D</td>
<td></td>
<td>0.72</td>
<td>0.42</td>
<td>0.54</td>
<td>0.63</td>
</tr>
</tbody>
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EQ-5D, EuroQol EQ-5D; VAS, visual analog scale.

Table 1. Quality of Life Estimates for Various Critical Limb Ischemia-Related Clinical States
the Circulase I\textsuperscript{62} and II\textsuperscript{63} trials, and the Bypass vs Angioplasty in Severe Ischaemia of the Leg [BASIL] trial\textsuperscript{64}. In this meta-analysis, the reported clinical endpoints — which were offered as performance goals for use in subsequent single-arm studies of limb salvage — 1 year after infrainguinal bypass were as follows:

1. Patient survival was 85.7% (95% CI 83.3% to 88.1%) (It should be noted that most of the mortality that occurs during the first year and beyond appears to be from cardiovascular causes. The most accurate estimate of the perioperative mortality rate is 2.6%, based on the objective performance goals suggested by Conte and colleagues.\textsuperscript{65})

2. Amputation-free survival was 76.5% (95% CI 73.7% to 79.5%).

3. Limb salvage rate was 88.9% (95% CI 86.7% to 91.1%) at 1 year.\textsuperscript{65}

Based on these rates, the actual proportion of patients who undergo major amputation within 1 year of surgical revascularization is 9.5% (see Appendix 2 [online only] for methodology of deriving this estimate). These trials do not provide follow-up data beyond 1 year, but many other large studies with long-term follow-up suggest that the incidence of major amputation decreases to a low baseline rate beyond the first year after revascularization.\textsuperscript{59,66}

Efforts required to maintain graft patency are not as often detailed in published reports but are common and worthy of consideration when evaluating the cost and effectiveness of revascularization strategies. In PREVENT III, 22.3% of patients underwent reintervention within the first postoperative year.\textsuperscript{61} In the BASIL trial, a 26.0% rate of reintervention (either operative or endovascular) was seen among the 200 patients who underwent surgical bypass as the index revascularization procedure.\textsuperscript{64} These direct estimates of reintervention are comparable to estimates that can be calculated based on the difference between reported primary and secondary patency rates alone (see methodological details as described in Appendix 2–4, online only) and to other observational studies that report reintervention rates.\textsuperscript{67}

**Functional outcomes, discharge disposition, and quality of life after infrainguinal bypass**

In contrast to the countless studies that have focused on patency, most of what we know of the functional outcomes and discharge disposition after infrainguinal bypass is based on a small number of publications. In all, these studies suggest that infrainguinal bypass is quite good at maintaining the ability to ambulate and live independently. Specifically, among patients who were independently living and ambulatory before bypass, 96.3% remained so 6 months after the operation.\textsuperscript{68} Other authors have demonstrated that the ability to remain ambulatory after bypass is durable.\textsuperscript{69} Likewise, the ability to continue living independently is good. Although 28.7% of surviving patients are initially discharged to an intermediate care facility after bypass for CLI, this is appears to be for a brief period of postoperative rehabilitation; the proportion of patients who live independently returns to baseline within 1 year after bypass.\textsuperscript{20} Unlike patients undergoing major amputation, it does not appear that there is significant interaction between the postoperative pedal wound healing, postoperative ambulatory ability, and ultimate discharge disposition in the context of infrainguinal bypass.\textsuperscript{20,66,68,70,71} So based on these estimates, various patient-centered outcomes might be expected to have the following initial probabilities: 69.2% ambulatory and living independently; 27.9% ambulatory and initially discharged to an intermediate care facility; 2.9% nonambulatory and living independently; and 0.8% nonambulatory and living at an intermediate care facility.

Many studies have assessed quality of life after infrainguinal bypass; only few have used quality of life instruments useful in the context of cost-effectiveness studies (instruments useful for their ability to calculate quality-adjusted life-years, or QALYs).\textsuperscript{40,72} The findings of studies that have used such instruments are summarized in Table 1. In general, the quality of life among patients with CLI is significantly impaired, regardless of treatment strategy or outcome. This is likely related to the high incidence of systemic comorbidities found in this patient population (including cerebrovascular disease, heart failure, and/or coronary artery disease).\textsuperscript{61,64} Yet it is obvious that the quality of life among patients who have undergone surgical bypass seems to be consistently higher than among those who have an active foot ulcer or who have undergone major amputation (Table 1).

**Costs of infrainguinal bypass**

Many studies have detailed the costs of infrainguinal bypass, typically in comparison to major amputation (Table 2). Unfortunately, most of these studies are now more than a decade old and they utilize suboptimal sources of cost data such as Medicare claims or hospital charges. Similar to the quality-of-life data described previously, the relationship between average costs in these studies nevertheless seems relatively consistent: surgical revascularization appears consistently less costly than primary amputation but more costly than endovascular intervention. Clearly more contemporary costs estimates are needed from US medical centers, preferably using methodology such as microcosting,\textsuperscript{86} activity-based accounting,\textsuperscript{87} or transition cost accounting.\textsuperscript{88}
Outcomes after endovascular intervention

Mortality and limb salvage after endovascular intervention for CLI

The use of endovascular interventions in the United States has increased more than 3-fold over the previous decade, and endovascular intervention, which most often includes percutaneous angioplasty of infrainguinal arteries with or without stent placement and occasionally percutaneous atherectomy, is increasingly used as a first-line treatment for patients with CLI. Attempts to demonstrate the benefit of these endovascular interventions are often made by comparing endovascular outcomes with surgical bypass outcomes, but the large degree of heterogeneity (in lesion level, length and characteristics, in patient comorbidities and functional status, and in treatment characteristics) has made these comparisons difficult. Nonetheless, several informative studies do exist.

In the BASIL trial, 452 patients with “severe limb ischemia” (a patient population that would include those with CLI as well as less severe “subcritical limb ischemia”) who appeared to be suitable candidates for either endovascular or surgical revascularization were randomized to either an endovascular revascularization-first or surgical revascularization-first strategy. Subsequent crossover between the 2 treatment arms was allowed. At the end of the 5-year follow-up period, there was no difference in overall amputation-free survival between the 2 groups, but a higher overall survival rate and a trend toward an improved amputation-free survival rate were seen among the subset of patients assigned to bypass first who survived 2 or more years after randomization. Neither the early (30-day) postprocedural mortality rates (3.0% and 5.6% for the endovascular and bypass groups, respectively) nor the long-term (5-year) survival rates (45.1% and 48.2%, respectively) differed significantly between the 2 strategies.

Many aspects of the BASIL trial limit the generalizability of its findings, including the inclusion of patients with subcritical limb ischemia, the low proportion of patients with CLI that were eligible for and ultimately enrolled in the trial, the crossover between assigned treatments, and the choice of amputation-free survival as a primary end-point. Additionally, we emphasize that the CLI patient population in the US is quite different from the study population in BASIL. Specifically, US patients have a higher prevalence of diabetes and end-stage renal disease, are more often non-Caucasian, and have a higher burden of infrapopliteal (rather than femoral) occlusive disease, all parameters which are known to affect the clinical endpoints studied in BASIL. Furthermore, the drastically different health care delivery system and the rare use of stents (placed in just 2% of BASIL trial participants) are 2 important factors that limit the relevance of the economic analysis in this trial to US clinicians and policy makers.

Superficial femoral artery lesions are among the most common targets for infrainguinal endovascular intervention, and good quality data on the outcome of these interventions are provided by 2 randomized trials. These trials, which compared the outcomes of angioplasty with or without stenting, report 1-year angiographic or ultrasonographic evidence of restenosis rates of 31.7% and 37%. Similarly, a comprehensive review by Inhat and

Table 2. Average Reported Costs of Managing Critical Limb Ischemia

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Primary amputation, $</th>
<th>Surgical revascularization, $</th>
<th>Endovascular intervention, $</th>
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<tr>
<td>Heller, 1981 (cited in Perler)</td>
<td>71,981</td>
<td>56,018</td>
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<tr>
<td>Auer, 1983</td>
<td>27,131</td>
<td>19,806</td>
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<tr>
<td>Mackey, 1986</td>
<td>35,673</td>
<td>11,316</td>
<td></td>
</tr>
<tr>
<td>Raviola, 1988</td>
<td>49,266</td>
<td>40,490</td>
<td></td>
</tr>
<tr>
<td>Gupta, 1988</td>
<td>49,383</td>
<td>47,513</td>
<td></td>
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<tr>
<td>Cheshire, 1992</td>
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<tr>
<td>Hunink, 1994</td>
<td>41,849</td>
<td>29,382</td>
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<tr>
<td>Johnson, 1995</td>
<td>35,105</td>
<td>15,481</td>
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<td>Singh, 1996</td>
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<td>15,273</td>
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<tr>
<td>Eneroth, 1996</td>
<td>8,400</td>
<td>5,997</td>
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<tr>
<td>Luther, 1997</td>
<td>101,228</td>
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<tr>
<td>Panayiotopoulos, 1997</td>
<td>33,807</td>
<td>11,473</td>
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<tr>
<td>Werneck, 2009</td>
<td>18,318</td>
<td>3,012</td>
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<td>Forbes, 2010</td>
<td>36,584</td>
<td>27,572</td>
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<tr>
<td>Jaff, 2010</td>
<td>16,244</td>
<td>11,169</td>
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Reported monetary values have been converted to 2009 USD equivalents for relevance to the reader. Because of heterogeneity of the practice settings and the methodology for calculating costs, these average costs may not be directly comparable. Finally, what are reported as “costs” in some studies may in fact actually have represented charges.
than for bypass surgery for patients with CLI. Indeed, with this, limb salvage rates seem lower for an angioplasty of 841 CLI patients who underwent open or endovascular surgery at 5 years for saphenous graft conduits. Consistent primary and primary-assisted patency rates of 76% to 94% do not seem as durable as femoral to above-knee bypass surgery for lesions of greater than 5 cm. By comparison, these results are independent. This publication, describing a cohort of CLI patients who underwent angioplasty with the outcomes of 2,653 limbs in 2,557 patients with tissue loss and lower extremity occlusive disease.117-121 On the other hand, revascularization alone may not lead to wound healing, and major amputation may be needed in 2% to 7% of patients with a patent infrapopliteal bypass graft.6,98,122 leading at least a few authors to suggest that the importance of revascularization was not an important determinant factor for either postintervention ambulatory ability or independent living status.

Quality of life after surgical and endovascular revascularization has been described using many global and disease-focused instruments. For the purposes of providing a framework for future cost-effectiveness studies, only a few studies use global quality-of-life instruments, which provide numbers that can be translated to quality-adjusted life years. The largest of these was the Dutch Bypass, Oral anticoagulants, or Aspirin (BOA) study by Tangelder45 (the results of which were further clarified in the rectification by Busschbach46). Patients in this study with a patent bypass graft had a mean EQ-5D\text{index} score of 0.63, notably higher than scores of patients who underwent primary amputation or secondary amputation after failed bypass (scores of 0.43 and 0.33, respectively). Other studies using the EuroQol have shown comparable EQ-5D scores.68,112

The quality-of-life data from the BASIL trial are notable for having data collection limited to the first 3 years after randomization and having 32% missing data; nonetheless it is the only study to use the EuroQol to describe the quality of life of patients undergoing endovascular intervention. In this trial, the EQ-5D\text{index} scores were 0.56 at 1 year for patients undergoing endovascular-first intervention compared with 0.62 for those undergoing surgical bypass first, a difference that was not significant.

Wound healing after revascularization

Sufficient oxygen and nutrient delivery to the foot through revascularization is clearly important to patients with tissue loss and lower extremity occlusive disease.117-121 On the other hand, revascularization alone may not lead to wound healing, and major amputation may be needed in 2% to 7% of patients with a patent infrapopliteal bypass graft,6,98,122 leading at least a few authors to suggest that the importance of revascularization in the healing process may be overestimated.123-125 Yet the healing of foot wounds is important because they consume time and effort (minor amputations, wound debridements, and/or skin grafting are needed in nearly half of patients who undergo infrapopliteal bypass for ischemic ulcers126) and because they appear to adversely influence limb salvage, ambulatory function, and ability to live independently.
Among 334 patients described by Chung and colleagues that underwent infrarenal bypass for CLI, 82% patients who initially had “mild” pedal necrosis (defined as either a plantar ulcer over metatarsal heads or digital necrosis) and only approximately 50% of patients who initially had “severe” pedal necrosis (defined as multiple plantar ulcers overlying metatarsal heads or wounds at the midfoot, heel, malleoli, or calf) had complete wound healing at 1 year. Nearly identical results are reported by the University of Arizona Health Sciences Center group. If one assumes that wound healing will continue at the constant rate described in the 1-year results by Chung and colleagues, complete wound healing rates may reach 90% by 2 years in patients with mild pedal necrosis and 65% to 70% by 2 years in patients with moderate pedal necrosis. Endovascular intervention does appear quite capable in augmenting foot perfusion (viz. oxygen and nutrient delivery), but it may augment it to a smaller degree than surgical revascularization. So it follows that wound healing may be slower and less complete after endovascular intervention than after surgical revascularization, at least for large or complicated foot wounds. A recent presentation by the Georgetown University Limb Salvage group suggests that this may indeed be the case: among patients who underwent lower extremity intervention for tissue loss, the median time to healing was shorter among bypass patients (98 days) than among endovascular intervention patients (132 days). The incidence of total amputations and major amputations during follow-up was lower in the surgical bypass group than in the endovascular intervention group: 20% vs 7%, respectively, for total amputation and 8% vs 2.8% for major amputations, respectively. Among the subset of patients with wounds larger than 2 cm, complete wound healing occurred in 70.2% by day 115 after surgical bypass but in only 27.1% by day 162 after endovascular intervention. These rates appear comparable to the 40% wound healing rate at 10 months seen in the series of tibial angioplasty by Fernandez and coworkers. If extrapolated under the assumption of a constant rate of wound healing, the wound healing rate based on these data would be approximately 60% at 1 year for wounds greater than 2 cm.

Outcomes after primary amputation

Traditional clinical outcomes

Major amputation is most often reserved for patients who have active sepsis and foot necrosis extensive enough to preclude attempts at limb salvage. In other circumstances, major amputation is performed when attempts at revascularization (surgical or endovascular) have failed, when the extent of dry necrosis is thought to preclude limb salvage, and when conduit for bypass is limited or unavailable, and when there is an inadequate distal target or outflow for bypass. Furthermore, when a patient is nonambulatory at baseline, postoperative amputation is unlikely; this too is sometimes used as a contraindication to limb salvage attempts. Finally, the presence of a severe comorbidity that leads to excessive perioperative risk (or at least the perception thereof) is also often used as a contraindication to limb salvage attempts and an indication for primary amputation. The perioperative mortality associated with major lower extremity amputation has been reported to be 7% to 11%. Although this is clearly higher than the perioperative mortality associated with infrarenal surgical revascularization, amputation has traditionally been perceived as a lower risk procedure than surgical revascularization, the higher mortality rate being attributed to the higher prevalence of comorbid conditions in patients undergoing major amputation. To estimate the degree to which perioperative mortality is associated with medical comorbidities vs the operation itself (and associated perioperative stress), our group examined a high-risk cohort of patients undergoing infrarenal revascularization or major amputation. After the use of propensity scoring to obtain 2 cohorts matched on presence and severity of high-risk comorbidities, we found that lower extremity revascularization was in fact not associated with higher 30-day mortality or major morbidity than major amputation. Indeed, there was a small but statistically significant survival benefit associated with infrarenal bypass (93% vs 90%, p = 0.015). These findings demonstrate that although the perioperative mortality rate is high in these high-risk patients, revascularization actually appears to have a lower mortality rate than major amputation when the burden of comorbidities is balanced between the 2 groups.

Functional outcomes, discharge disposition, and postoperative wound problems of the CLI amputee

As outlined in a systematic review by Sansam and associates, the proportion of patients who have the ability to ambulate on a prosthetic after major amputation is highly variable and greatly affected by the heterogeneity of patients in that cohort. As might be expected, patients who undergo major amputation for ischemia are less likely to ambulate than those who undergo amputation for trauma or other nonischemic causes, but the amputation rate does not appear significantly affected by whether the amputation is primary or secondary (ie, done after a failed revascularization). The series that appears most informative for estimating ambulatory status after major amputation for ischemia is that of Taylor and colleagues, which describes a cohort of 553 patients followed for a period up to 2 years. In this series, the ability to ambulate was 61% at 3 months,
In the report by Nehler and colleagues, 21 17% of patients who had previously lived independently were not able to do so one year after amputation. With time, this percentage increased slightly (31% at 2 years). Among the 5 reports that allowed the total number of ambulatory patients to be calculated, there were 526 ambulatory patients among the 1,015 patients (52% overall). 21,138-141

It should be noted that most studies reporting ambulation after major amputation do not differentiate between below-knee (transtibial) and above-knee (transfemoral) amputees. 16% of patients were nonambulatory preoperatively and 49% were nonambulatory postoperatively at 10.3 months. Among the 5 reports that allowed the total number of ambulatory patients to be calculated, there were 526 ambulatory patients among the 1,015 patients (52% overall). 21,138-141

Many patients previously living independently are discharged to a rehabilitation or intermediate care facility after a major amputation. In the series by Taylor and colleagues, 138 27% of patients who had previously lived independently were not able to do so one year after amputation. With time, this percentage increased slightly (31% at 2 years). In the report by Nehler and colleagues, 21 17% of patients were living in an intermediate care facility at 10 months. In contrast to the small increase seen in the Taylor series, the number in the Nehler series decreased over time to 8% by 17.5 months. It is not clear whether the changes in this latter series represent a true transition from intermediate care facilities to independent living or whether a higher mortality rate among patients living in intermediate care facilities lead to nonrandom censoring and affected estimates. Because of the specificity of the Nehler estimates (that the patients described were known to have been living in the community before the amputation), we recommend using a 17% incidence of discharge to a rehabilitation or intermediate care facility after major amputation for cost-effectiveness analysis.

Although major amputations eliminate foot wounds, other wound healing problems may persist after discharge. Healed wounds were present in 83% of above-knee amputations and 85% of below-knee amputations in the Nehler series at 200 days, for an overall average of 84%. Figure 1 of the manuscript suggests that there are no open wounds remaining past 1 year, but it should be noted that only 1 patient remained in follow-up past this time point. In an older study by McWhinnie and colleagues, 142 the incidence of stump healing problems after primary below-knee amputation was 45% before 1984 and 25% between 1984 and 1994. Similarly, Peng and Tan 139 reported a 19% incidence of postoperative wound infections and an 8% rate of conversion from below-knee to above-knee amputation. For the purposes of cost-effectiveness, evaluations would recommend a 16% incidence of open wounds during the first year after major amputation.

Patients with open wounds are unlikely to ambulate on a prosthesis after major amputation. In addition, ambulatory status appears to have some effect on likelihood of discharge to an intermediate care facility (53.4% of nonambulatory patients vs 22.1% of ambulatory patients). 21 Although it is likely that some patients with open wounds will ambulate with a prosthesis once the wound has healed, for the purposes of a modeling or simulation, open wounds should be distributed only among nonambulatory patients. (Note that this simply changes the distribution of open wounds for the purposes of simplifying the model and does not change the overall number, costs, or any other parameter.) So, expected outcomes after major amputation might be summarized as follows: 48.2% of patients are ambulatory with a prosthesis and living independently; 7.3% are ambulatory with a prosthesis and living at an intermediate care facility or nursing home; 10.3% are nonambulatory, living independently, with an open wound early after amputation; 16.9% are nonambulatory, living independently, with healed wounds; 6.7% are nonambulatory, living at an intermediate care facility, with open wound early after amputation; and 10.6% are nonambulatory, living at intermediate care facility, with healed wounds.
Table 3. Functional Outcomes of Patients Undergoing Major Amputation for Critical Limb Ischemia

<table>
<thead>
<tr>
<th>First author</th>
<th>Alive at follow-up, n</th>
<th>Percent ambulatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor</td>
<td>553</td>
<td>55</td>
</tr>
<tr>
<td>Necler</td>
<td>154</td>
<td>49</td>
</tr>
<tr>
<td>Remes</td>
<td>119</td>
<td>33</td>
</tr>
<tr>
<td>Hermodsson</td>
<td>112</td>
<td>63</td>
</tr>
<tr>
<td>McWhinnie</td>
<td>100</td>
<td>41</td>
</tr>
<tr>
<td>Peng</td>
<td>38</td>
<td>15</td>
</tr>
<tr>
<td>Total/overall percentage</td>
<td>1,015</td>
<td>52</td>
</tr>
</tbody>
</table>

Quality of life after major amputation in CLI patients

As part of the United Kingdom Prospective Diabetes Study (UKPDS 62), Clarke and colleagues\(^\text{14}\) used the EuroQol EQ-5D on 3,676 diabetic patients and used regression analyses to determine the impact of diabetic complications on quality of life. The mean EQ-5D tariff score for patients without complications was 0.785. Amputation was estimated to reduce the EQ-5D tariff score by 0.280 in the final marginal effects model, more than any of the other examined complications (including myocardial infarct, ischemic heart disease, heart failure, stroke, and blindness). This would result in an EQ-5D of 0.51 in patients with a major amputation. Other studies have found mean EQ-5D values ranging from 0.31 to 0.62.\(^\text{45,47,49-51}\) For the purposes of cost-effectiveness evaluations, a value of 0.54, the weighted mean of these studies (Table 3), appears to be a reasonable estimate. Finally, a stay in a nursing home or intermediate-care facility does not appear to have a major impact on quality of life.\(^\text{149,150}\)

Costs of major amputation

In the early to mid 1990s several groups compared the costs of primary amputation with surgical revascularization (Table 2). These reports are from widely varying health care environments in several different countries and the methodologies are very heterogeneous in the ways they estimated costs. Furthermore, most were published more than a decade ago. Nonetheless, it is notable that across all health care settings—and in spite of differences in cost-accounting methodologies—primary amputation was found to be more expensive than surgical revascularization in every study that compared these procedures.

The costs associated with amputation clearly extend beyond the initial hospitalization. Amputees who do eventually return home face the costs associated with modifying their home with equipment (railings, ramps, etc) that help achieve mobility.\(^\text{80}\) During an 8-year period of follow-up among 112 Swedish CLI patients who underwent below-knee amputation, 71 (63%) of patients had been fitted with a prosthesis. Among these, the median per patient costs associated with the prosthesis (including the costs of the prosthesis itself, sockets, and maintenance) for this 8-year period was the 2009 USD equivalent of $2,586. In the US, current prosthetic costs typically are significant. The calculated costs for a 7-year period (including initial prosthesis and amortized replacement cost plus the costs of associated equipment) is, in 2009 USD, $13,822 for a below-knee prosthesis, $26,937 for a through-knee amputation, and $29,132 for an above-knee prosthesis.\(^\text{145}\) The outpatient costs for patients who lose their ability to ambulate may be higher if one includes the costs of handrails, wheelchair ramps, wheelchair-amenable transportation, and other accommodations for the amputee living at home, and even higher still for those unable to live at home and in need of institutionalization in a nursing home.

Impact of systemic comorbidities among CLI patients

The relationship between the presence and severity of peripheral arterial disease and the risk of death (most of which is cardiovascular in cause) has been well documented,\(^\text{146-150}\) and the high prevalence of survival-limiting comorbidities should be considered when weighing the risks and benefits of various management strategies.\(^\text{151}\) Reliable estimates of the annual mortality rate of a general CLI cohort may be derived from the BASIL, PREVENT III, and Circulase trials: 87% at 6 months in the Circulase trial,\(^\text{63}\) 84.4% at 1 year in the PREVENT III trial,\(^\text{61}\) and 46% at 5 years in the BASIL trial.\(^\text{152}\) These survival rates are remarkably consistent with observational studies of CLI patients.

Conclusions

As is evidenced by this review, there is a rich body of literature detailing the clinical outcomes of infragenual bypass, endovascular intervention, and major amputation for CLI, as described by the traditional endpoints of patency, limb salvage, and mortality. The amount of literature describing results in terms of patient-oriented outcomes or global quality-of-life measures is adequate, but contemporary, high quality applicable cost data obtained from US medical centers are lacking. In addition, although clinical guidelines do exist, few studies have attempted to combine clinical results, patient-oriented outcomes, and cost data in a systematic and comprehensive fashion to allow for management strategies (or perhaps health policy) to be guided and well informed.

US vascular surgeons have been relentless in evaluating important health technologies with multicenter randomized trials\(^\text{153-157}\) and have worked to establish many consensus guidelines for patient care.\(^\text{158-162}\) Many have also become leaders in the recent patient safety, quality, and...
patient-oriented outcomes movement in medicine.\textsuperscript{47,139-142} The next major challenge for US vascular surgeons will be to carry on in our mission of providing outstanding personalized care and ensuring excellent outcomes while finding ways to minimize the costs of such care\textsuperscript{5}; in other words, optimizing the “value” of health care interventions we provide to our patients.\textsuperscript{19} This will be important not only to justify the existence of the health care programs in which vascular surgeons participate but also to ensure that such programs are accessible to everyone. Although the experiences and studies of non-US medical centers may be insightful, the fundamental differences in health care access and delivery suggest that the most relevant studies should be based on US patient populations, medical centers, and providers. Cost-effectiveness studies using mathematical models and probabilistic sensitivity analyses can be critical tools in this mission because they summarize the current state of our knowledge, allow the simulation and comparison of various strategies or interventions, and provide at least some basis for making decisions that cannot wait for the results of the next multicenter, prospective randomized trial.\textsuperscript{163}

In addition to the evaluation of cost-effectiveness, there are many other potential benefits to modeling the cost-effectiveness of limb salvage management strategies. A cost-effectiveness model identifies areas of uncertainty where further research efforts may help improve patient care, and may even allow the potential cost or cost-savings gained from the additional research to be quantified.\textsuperscript{164} Although they do not take the place of randomized trials, cost-effectiveness models can help future clinical trials through predicting the global outcomes, or estimating the trial costs.\textsuperscript{165} Finally, a careful analysis of costs within the context of a cost-effectiveness model can help identify important cost drivers and potential areas of cost savings.

In summary, much of the effort in limb salvage has focused on patenty and revascularization, with little or no attention on the financial costs, global quality of life, wound healing, or functional outcomes of these efforts. It is clear from this review that more high quality publications focusing on patency and revascularization, with little or no attention on the financial costs, global quality of life, wound healing, or functional outcomes of these efforts. It is clear from this review that more high quality publications focusing on patency and revascularization, with little or no attention on the financial costs, global quality of life, wound healing, or functional outcomes of these efforts. It is clear from this review that more high quality publications focusing on patency and revascularization, with little or no attention on the financial costs, global quality of life, wound healing, or functional outcomes of these efforts. It is clear from this review that more high quality publications focusing on patency and revascularization, with little or no attention on the financial costs, global quality of life, wound healing, or functional outcomes of these efforts. It is clear from this review that more high quality publications focusing on patency and revascularization, with little or no attention on the financial costs, global quality of life, wound healing, or functional outcomes of these efforts. It is clear from this review that more high quality publications focusing on patency and revascularization, with little or no attention on the financial costs, global quality of life, wound healing, or functional outcomes of these efforts. It is clear from this review that more high quality publications focusing on patency and revascularization, with little or no attention on the financial costs, global quality of life, wound healing, or functional outcomes of these efforts. It is clear from this review that more high quality publications focusing on patency and revascularization, with little or no attention on the financial costs, global quality of life, wound healing, or functional outcomes of these efforts. It is clear from this review that more high quality publications focusing on patency and revascularization, with little or no attention on the financial costs, global quality of life, wound healing, or functional outcomes of these efforts. It is clear from this review that more high quality publications focusing on patency and revascularization, with little or no attention on the financial costs, global quality of life, wound healing, or functional outcomes of these efforts. It is clear from this review that more high quality publications focusing on patency and revascularization, with little or no attention on the financial costs, global quality of life, wound healing, or functional outcomes of these efforts. It is clear from this review that more high quality publications focusing on patency and revascularization, with little or no attention on the financial costs, global quality of life, wound healing, or functional outcomes of these efforts. It is clear from this review that more high quality publications focusing on patency and revascularization, with little or no attention on the financial costs, global quality of life, wound healing, or functional outcomes of these efforts.

**Appendix 1. The Model to Optimize Healthcare Value in Ischemic Extremities (MOVIE)**

**Study Collaborators**

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**Author Contributions**

Study conception and design: Barshes, Belkin

Acquisition of data: Barshes, Belkin

Analysis and interpretation of data: Barshes, Belkin

Drafting of manuscript: Barshes

Critical revision: Belkin

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Appendix 2. Details of Methodology and Application to Future Models of the Cost-Effectiveness of Managing Limb Ischemia

The objective of this study was to comprehensively review the clinical outcomes, patient-oriented outcomes (including quality of life and ability to ambulate), and costs associated with various management strategies for chronic critical limb ischemia with tissue loss, with the ultimate goal of creating a detailed and robust decision-analytic model of the cost-utility relationship (ie, cost-effectiveness) of these management strategies. A comprehensive literature review was undertaken. Relevant manuscripts were first identified through PubMed, the updated Trans-Atlantic Inter-Society Consensus (TASC II) Document on Management of Peripheral Arterial Disease, and three randomized clinical trials focused on critical/subcritical limb ischemia: the Project of Ex-Vivo vein graft Engineering via Transsection III (PREVENT III)\(^1\), the Circulase I \(^3\) and II \(^4\) trials, and the Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial.\(^5\) Additional literature was identified through a review of the bibliographies from these initial manuscripts and others. Rather than reviewing every available publication, the focus of this review was relevant, high quality evidence (in accordance with the Oxford Centre for Evidence-Based Medicine Levels of Evidence for describing the prognosis of disease states, outcome of therapy, or economic and decision analysis\(^6\)). As such we preferentially focused on studies of patients with chronic ischemia and tissue loss (Rutherford category 5) whenever possible; when such studies were not available or were poor quality, studies of patients with any form of critical limb ischemia (ie, tissue loss or rest pain alone) were included.

Defining the Probabilities of Clinical Events

Among the fundamental features of decision analytic models is modeling the occurrence of events or clinical states based on known or estimated probabilities\(^7\). In the context of Rutherford 5 critical limb ischemia, the achievement of limb salvage — or “preservation of some or all of the foot” (ie, avoidance of major amputation)\(^1\) — is of obvious importance. The manner in which limb salvage is conventionally reported, however, requires some translation for use in a decision analytic model. For the purposes of a decision analytic model, the amputation probability should be defined as the number of patients who are both alive and have undergone major amputation by a given point in time divided by the total number of patients who are both alive and have undergone major amputation (ie, tissue loss or rest pain alone) were included. This is similar (but not identical to) limb salvage, a proportion comprised of the number of living patients who have avoided major amputation up to any given point in time divided by the total number of patients alive at that time point in time. The amputation-free survival rate refers to the proportion of patients that have avoided major amputation and death up to any given point in time. To summarize, these three terms have the following definitions:

- Amputation probability = patients with major amputation/(alive patients + dead patients)
- Limb salvage = patients without major amputation/alive patients
- Amputation-free survival [AFS] = (all patients – deaths – major amputations)/all patients

As a means to demonstrate the relationship between these variables, consider 100 patients who undergo a management strategy that has, at a time point 365 days after the procedure, resulted in 20 patients who are dead, 60 patients who have preserved their foot, and 20 patients who have required major amputation. At one year, this management strategy has an amputation probability of 20%, a limb salvage rate of 75%, and an amputation-free survival rate of 60%. Although amputation-free survival and limb salvage continue to be used as conventional endpoints in vascular surgery literature, it is the amputation probability that is needed for use in a Markov model of critical limb ischemia.

Patency is another important clinical state that is conventionally described using the recommended standard terminology approved by the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery.\(^8\) This terminology includes “primary patency”, which is defined as “uninterrupted patency with either no procedure performed on it or a procedure . . . to deal with disease progression in the adjacent native vessel”, whereas secondary patency applies to grafts in which patency is “restored after occlusion by thrombectomy, thrombolysis, or transluminal angioplasty, and/or any problems with the graft itself or one of its anastomoses require revision or reconstruction.” While the total number of graft revisions is rarely reported, it may be estimated by dividing the difference between the primary and secondary patency rates by the success rate of revision, then multiplying this by the amputation-free survival rate.

Thus, the traditional, patency- and limb salvage-based reporting measures should instead be translated to the following four patient-oriented, cost-considerate states for the purposes of this decision analysis:
● **Dead:** including perioperative/periprocedural deaths and deaths from all other causes.

● **Alive with (major) amputation:** amputation at the level of the ankle or above.

● **Alive with revision:** includes both successfully-revised grafts/vessels with reintervention and asymptomatic occlusions that have undergone attempts at revision.*

● **Alive without revision or amputation:** includes grafts/vessels without attempted revision or reintervention and asymptomatic occlusions that have not been intervened upon.

As an example, consider the placebo group one-year outcomes as reported in the PREVENT III trial. The reported endpoints included a survival rate of 84.4%, a limb salvage rate of 89.2%, a primary patency rate of 59.5%, and a secondary patency rate of 77.5%. From Berceli we estimate the success rate of revision attempts to be approximately 65.8%. Thus, true proportions of patients in various clinical states one year after an index surgical bypass are:

- **Dead** = 1 – survival rate = 15.6%
- **Alive with major amputation** = (1 – limb salvage) × survival rate = (1.00-0.892) × 0.844 = 9.1%
- **Total alive without amputation** (ie, ± revision) = limb salvage × survival rate = 0.892 × 0.844 = 75.3%
  - **Alive with revision** = [(2nd patency – 1st patency)/success rate] × total alive without amputation = [(0.775 – 0.595)/0.658] × 0.753 = 20.6%
  - **Alive without revision** = total alive without amputation – alive with revision = 0.753–0.209 = 54.7%

With a total study population of 1,404, the above-calculated proportions would estimate that 289 patients were alive with revision. This estimate corresponds reasonably well to the 316 patients described in Berceli as having actually undergone revision.⁹

Three additional factors have an important impact on patient-oriented quality of life, subsequent clinical outcomes, and cost: the ability to ambulate (with or without a limb prosthesis, walker, cane or other aid), discharge disposition (ability to live independently versus need for an intermediate care facility, rehabilitation facility, or nursing home), and the presence of any ongoing wound care needs (viz., presence of closed versus open wounds).¹⁰-¹⁵ Thus, within each of the above categories except “dead”, hypothetical patients will be assigned to one of up to eight subcategories (three factors, each with two outcomes, with some categories collapsed for simplification if subtotals are small). This will help in further specifying outcomes and quality of life which may be expected from a meaningful, patient-oriented perspective, as well as further specifying costs.

**Global Measures of Health Utility**

Each of the above-mentioned patient-oriented/clinical states will be associated with a health utility measure to help further quantify its meaningfulness to patients. Although disease-specific quality of life instruments exist for limb ischemia¹⁰,¹⁶,¹⁷, global measures of health utilities are the preferred quantitative assessment of a patient’s preferences for a given health outcome.¹⁸ Furthermore, certain global measures, such as the Health Utilities Index¹⁹ and the EuroQol²⁰, provide results using ratio scales which can be converted to quality-of-life indices and, when combined with survival data, to quality-adjusted life-years (QALYs).¹⁸ While the use of QALYs does have some limitations²¹, it is generally regarded as single best measure of health that can be used across disease states.²⁰,²² In the current study, global measures of health utility will assigned to each health state based on a comprehensive review of published quality of life studies in the critical limb ischemia population. As is the convention in cost-utility and cost-effectiveness analyses, future health utilities will be discounted at a 3% rate.¹⁸

*Note: Although major amputation does have a significant impact on quality of life (see following), there is no evidence to suggest the existence of any important differences in clinical outcomes, quality of life, or costs between patients undergoing “major reinterventions” such as new surgical bypass grafts or thrombectomy/thrombolysis and those undergoing “minor reinterventions” such as patch angioplasty, percutaneous transluminal angioplasty or stenting; thus the definition of “Major Adverse Limb Event” [MALE], as proposed by Conte et al²³ has not been incorporated into the current study.
## Appendix 3. Recommended Baseline Values and Distributions for Parameters Important to the Modeling of Outcomes of Managing Rutherford Category 5 Critical Limb Ischemia

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Baseline value</th>
<th>Recommended distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events affecting all patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline annual mortality rate</td>
<td>0.117</td>
<td>Beta (80.5, 607.6)</td>
<td>Conte\textsuperscript{23}</td>
</tr>
<tr>
<td><strong>Events after surgical revascularization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional periprocedural mortality, surgical revascularization</td>
<td>0.026</td>
<td>Beta (18, 679)</td>
<td>Conte\textsuperscript{2}</td>
</tr>
<tr>
<td>Limb salvage at one year following surgical revascularization</td>
<td>0.892</td>
<td>Beta (620, 87)</td>
<td>Conte\textsuperscript{2}</td>
</tr>
<tr>
<td>Probability of remaining alive but requiring major amputation by the end of the first year after surgical revascularization</td>
<td>1-limb salvage</td>
<td></td>
<td>See review text</td>
</tr>
<tr>
<td>Probability of remaining alive but requiring major amputation beyond the first year after surgical revascularization</td>
<td>0.026</td>
<td></td>
<td>See review text</td>
</tr>
<tr>
<td>Probability of remaining ambulatory</td>
<td>0.971</td>
<td>Beta (402, 12)</td>
<td>Abou-Zamzam\textsuperscript{24}</td>
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<tr>
<td>Probability of maintenance of independent living</td>
<td>0.986</td>
<td>Beta (412, 4)</td>
<td>Abou-Zamzam\textsuperscript{24}</td>
</tr>
<tr>
<td>Probability of initial discharge to intermediate care facility</td>
<td>0.287</td>
<td>Beta (371, 963)</td>
<td>Goodney\textsuperscript{25}</td>
</tr>
<tr>
<td>Probability of wound healing during one year</td>
<td>1.00</td>
<td></td>
<td>See review text</td>
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<tr>
<td><strong>Events after endovascular revascularization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional periprocedural mortality, endovascular revascularization</td>
<td>0.026</td>
<td>Beta (18, 679)</td>
<td>Equal to operative mortality per BASIL trial\textsuperscript{26}</td>
</tr>
<tr>
<td>Probability of remaining alive but requiring major amputation by the end of the first year after endovascular revascularization</td>
<td>0.122</td>
<td>Beta (17.8, 128.1)</td>
<td>See review text</td>
</tr>
<tr>
<td>Probability of remaining alive but requiring major amputation by the end of the subsequent year after surgical revascularization</td>
<td>0.026</td>
<td></td>
<td>See review text</td>
</tr>
<tr>
<td>Probability of requiring revision/reintervention after endovascular revascularization</td>
<td>0.260</td>
<td>Beta (319, 1085)</td>
<td>See review text</td>
</tr>
<tr>
<td>Probability of requiring revision/reintervention after surgical revascularization</td>
<td>0.227</td>
<td>Beta (319, 1085)</td>
<td>Berceli\textsuperscript{7}</td>
</tr>
<tr>
<td><strong>Events after major amputation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional periprocedural mortality, major amputation</td>
<td>1.52x operative mortality</td>
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<td>See review text</td>
</tr>
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<td><strong>Events after local wound care</strong></td>
<td></td>
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</tr>
<tr>
<td>Annual probability of major amputation with local wound care alone</td>
<td>0.380</td>
<td>Beta (33, 55)</td>
<td>See review text</td>
</tr>
<tr>
<td>Annual probability of ulcer/wound healing with local wound care alone</td>
<td>0.410</td>
<td>Beta (14, 21)</td>
<td></td>
</tr>
<tr>
<td>Annual probability of recurrence after ulcer/wound healing with local wound care alone</td>
<td>0.610</td>
<td>Beta (42, 27)</td>
<td></td>
</tr>
<tr>
<td><strong>Utilities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Utility after amputation</td>
<td>0.54</td>
<td>Triangular (0.28, 0.52)</td>
<td></td>
</tr>
<tr>
<td>Utility after intact limb with healed wound</td>
<td>0.62</td>
<td>Beta (221, 136)</td>
<td>Forbes,\textsuperscript{27} review text</td>
</tr>
<tr>
<td>Utility after with intact limb and open wound</td>
<td>0.42</td>
<td>Triangular (0.28, 0.52)</td>
<td>See review text</td>
</tr>
<tr>
<td>Utility with spontaneous healing of a foot wound (ie, local wound care alone)</td>
<td>0.64</td>
<td>Beta (223, 126)</td>
<td>Forbes,\textsuperscript{27} review text</td>
</tr>
<tr>
<td>Utility of death</td>
<td>0.0</td>
<td></td>
<td>By convention</td>
</tr>
</tbody>
</table>
Appendix 4. Common Procedural Terminology Used to Identify and Categorize Interventions Done for Critical Limb Ischemia

<table>
<thead>
<tr>
<th>Procedure</th>
<th>CPT codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical revascularization</td>
<td></td>
</tr>
<tr>
<td>Femoropopliteal bypass with vein, prosthetic conduit, or in-situ</td>
<td>35556, 35656, or 35583</td>
</tr>
<tr>
<td>Femorotibial bypass with vein, prosthetic conduit, or in-situ</td>
<td>35566, 35666, or 35585</td>
</tr>
<tr>
<td>Distal origin grafts with vein, prosthetic conduits, or in-situ</td>
<td>35570, 35571, 35671, or 35587</td>
</tr>
<tr>
<td>Endovascular revascularization</td>
<td></td>
</tr>
<tr>
<td>Femoropopliteal or tibial vessel balloon angioplasty</td>
<td>35470 and 35474</td>
</tr>
<tr>
<td>Femoropopliteal or tibial vessel percutaneous atherectomy</td>
<td>35493 and 35495</td>
</tr>
<tr>
<td>Femoropopliteal or tibial vessel stent placement</td>
<td>37205 and 37206</td>
</tr>
<tr>
<td>Surgical revision of threatened / failing bypass grafts</td>
<td></td>
</tr>
<tr>
<td>Thrombectomy of arterial non-dialysis graft</td>
<td>35875 and 35876</td>
</tr>
<tr>
<td>Open revision of femoral Anastomosis of a synthetic arterial bypass graft</td>
<td>35883 and 35884</td>
</tr>
<tr>
<td>Endovascular revision of threatened / failing bypass grafts*</td>
<td></td>
</tr>
<tr>
<td>Percutaneous arterial thrombectomy</td>
<td>37184, 37185 and 37186</td>
</tr>
<tr>
<td>Femoropopliteal or tibial vessel balloon angioplasty</td>
<td>35470 and 35474</td>
</tr>
<tr>
<td>Femoropopliteal or tibial vessel percutaneous atherectomy</td>
<td>35493 and 35495</td>
</tr>
<tr>
<td>Femoropopliteal or tibial vessel stent placement</td>
<td>37205 and 37206</td>
</tr>
<tr>
<td>Diagnostic angiogram</td>
<td></td>
</tr>
<tr>
<td>Cannulation of aortic/pelvic/lower extremity arterial branches</td>
<td>36245, 36246, 36247</td>
</tr>
<tr>
<td>Major amputations</td>
<td></td>
</tr>
<tr>
<td>Above-knee amputation</td>
<td>27590 and 27592</td>
</tr>
<tr>
<td>Below-knee amputation</td>
<td>27880 and 27882</td>
</tr>
<tr>
<td>Minor amputations</td>
<td></td>
</tr>
<tr>
<td>Toe amputation</td>
<td>28825 and 28820</td>
</tr>
<tr>
<td>Mid-foot amputation</td>
<td>28810</td>
</tr>
<tr>
<td>Incision and drainage, simple or complex</td>
<td>10060 and 10061</td>
</tr>
<tr>
<td>Split-thickness skin grafts &lt;100 cm²</td>
<td>15100</td>
</tr>
<tr>
<td>Debridement below fascia</td>
<td>28003</td>
</tr>
</tbody>
</table>

Aortobifemoral bypass, iliofemoral bypass, femorofemoral bypass, axillofemoral bypass, or any type of endarterectomy, patch angioplasty, and profundaplasty was excluded unless it was done along with one of the above procedures at the same operation.

*Considered revision (in contrast to an endovascular revascularization) if done within a vein graft or prosthetic graft bypass.

REFERENCES


