A Framework for the Evaluation of "Value" and Cost-Effectiveness in the Management of Critical Limb Ischemia

Neal R Barshes, MD, MPH, Michael Belkin, MD, FACS, on behalf of the MOVIE Study Collaborators

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),[1] 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 <5 0 mmHg and/or toe pressure < 30 mmHg).[1,2] 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.[1,3,4] 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[5]), and may still result in limb loss in spite of a successful revascularization.[6]

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.[1] 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;[7] 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.[8] 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[9]), 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),[10] and this may increase further, to 8.3%, by 2030;[11] with projected population growth, this will represent approximately 29.8 million persons.[8] Further compounding the problem is the prediction that a larger proportion of this future US diabetic population is expected to be elderly.[11] Among patients with peripheral arterial disease and diabetes, the annual incidence of foot ulcers reaches 13.8%[12] and the risk of major amputation reaches 3.7% per year.[12] Foot care (including inpatient and outpatient wound care, treatment of infections, and ampu-

Disclosure Information: Authors have nothing to disclose. Timothy J Eberlein, Editor-in-Chief, has nothing to disclose.

The MOVIE Study Collaborators are listed in Appendix 1.

Received May 16, 2011; Revised July 11, 2011; Accepted July 14, 2011.
From the Division of Vascular and Endovascular Surgery, Department of Surgery, Brigham and Women's Hospital, Boston, MA.
Correspondence address: Michael Belkin, MD, FACS, Division of Vascular and Endovascular Surgery, Department of Surgery, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02215. email: mbelkin@partners.org

ISSN 1072-7515/11/$36.00
doi:10.1016/j.jamcollsurg.2011.07.011

Abbreviations and Acronyms

BASIL	= Bypass vs Angioplasty in Severe Ischaemia of the Leg trial
CLI	= critical limb ischemia
EQ-5D	= EuroQual-5D
PREVENT III	= Project or Ex-Vivo vein graft Engineering via Transfection III study

tations) is expensive[5] and represents the second highest cost driver among diabetic patients after dialysis.[13] Finally, major amputation has the biggest negative impact on quality of life among diabetic patients than any other complication.[14] 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),[15] many are calling for health care costs to be considered when deciding on treatment options.[16-18] Indeed, there are already indications that governmental and nongovernmental payers of US health care will take cost-effectiveness into consideration in coverage decisions.[18,19] The foundation for the management of CLI is based on the outcome parameters of interest to vascular surgeons—namely, target vessel patency[2] — and only recently have patient-oriented outcomes such as ability to ambulate[20,21] or quality of life[22] been taken into consideration. Only a few publications written in the past decade have examined the costs of limb salvage.[22,23] In a climate calling for decreased costs and improved "value,"[15] health care providers will be increasingly called on to provide economic justification for the continued existence of costly programs such as limb salvage centers. Although numerous high-quality, contemporary publications are available to examine the cost-effectiveness of management options for many clinical conditions (coronary artery disease[24-27] and heart failure,[28-32] for example), but only 2 cost-effectiveness analyses of limb salvage exist. Unfortunately both were published more than more than a decade ago, only one evaluated endovascular options, and neither considered the impact of patient-oriented outcomes.[33,34]

Herein we present a review of the impact of various management strategies for Rutherford 5 CLI on both the traditional clinical endpoints of patency and mortality as well as 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.[35-37] 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,[38] and the referral is often delayed or nonexistent.[39] There may be many reasons for a delay in or 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[40]) 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.[39,40]

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.[3] 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

Table 1. Quality of Life Estimates for Various Critical Limb Ischemia-Related Clinical States

First author	Instrument	No ulcer	Active ulcer	Major amputation	Surgical bypass	Endovascular intervention
Forbes[22]	EQ-5D		0.26–0.28		0.62	0.56
UKPDS[44]	EQ-5D	0.80		0.51		
Tangelder[45,46]	EQ-5D			0.51 (men) 0.43 (women)	0.61 (men) 0.53 (women)	
Davies[47]	EQ-5D				0.62–0.64	
Chetter[48]	EQ-5D					
Ragnarson Tennvall[49]	EQ-5D	0.60	0.44	0.31		
Ragnarson Tennvall[49]	VAS	0.64	0.52	0.54		
Larsson[50]	EQ-5D			0.62		
Redekop[51]	EQ-5D	0.84		0.62		
Sullivan[52]	Standard gamble			0.65		
Sprengers[53]	EQ-5D		0.34			
Van Hattum[54]	EQ-5D				0.68	
Weighted mean values		0.72	0.42	0.54	0.63	0.56

EQ-5D, EuroQol EQ-5D; VAS, visual analog scale.

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.[3] 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.[4,41,42] Norgren and colleagues,[4] for example, found a 50% major amputation rate at 12 months among placebo arm patients in a prostacyclin analog study, and Nikol and associates[43] found a major amputation rate of 33.9% at 12 months in a more recent study of plasmid-based gene therapy.[4]

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).[49] 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.[53]

Foot ulcers and nonhealing foot wounds have a significant financial impact as well. The well-cited report by Ramsey and colleagues[55] 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[56] based on a single US institution data and of $25,981 by Harrington and associates[57] 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.[58] Today it still remains the favored option of many vascular interventionalists, based predominately on the clinical outcomes associated with it.[1,59,60] 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,[61] the Circulase I[62] and II[63] trials, and the Bypass vs Angioplasty in Severe Ischaemia of the Leg [BASIL] trial[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.[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.[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.[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.[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.[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.[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.[68] Other authors have demonstrated that the ability to remain ambulatory after bypass is durable.[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.[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.[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).[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).[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,[86] activity-based accounting,[87] or transition cost accounting.[88]

Table 2. Average Reported Costs of Managing Critical Limb Ischemia

First author, year	Primary amputation, $	Surgical revascularization, $	Endovascular intervention, $
Heller, 1981 (cited in Perler[73])	71,981	56,018	
Auer, 1983[74]	27,131	19,806	
Mackey, 1986[75]	35,673	11,316	
Raviola, 1988[76]	49,266	40,490	
Gupta, 1988[77]	49,383	47,513	
Cheshire, 1992[78]	35,673	11,316	
Hunink, 1994[79]		41,849	29,382
Johnson, 1995[80]	35,105	15,481	
Singh, 1996[81]	27,325	15,273	
Eneroth, 1996[82]	8,400	5,997	
Luther, 1997[83]	101,228	56,478	
Panayiotopoulos, 1997[84]	33,807	11,473	
Werneck, 2009[23]		18,318	3,012
Forbes, 2010[22]		36,584	27,572
Jaff, 2010[85]		16,244	11,169

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.

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,[89-91] 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.[67,92-94] 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"[95]) 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.[64] 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.[96]

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 endpoint.[60] 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,[9,61,66,97] all parameters which are known to affect the clinical endpoints studied in BASIL.[3,97-101] 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.[22]

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%.[102,103] Similarly, a comprehensive review by Inhat and

Mills[104] demonstrated primary patency rates of 46% to 63% at 1 year for studies that reported average lesion lengths of greater than 5 cm. By comparison, these results do not seem as durable as femoral to above-knee bypass primary and primary-assisted patency rates of 76% to 94% at 5 years for saphenous graft conduits.[105-107] Consistent with this, limb salvage rates seem lower for an angioplasty than for bypass surgery for patients with CLI.[108] Indeed, the lower durability and higher reintervention rate of femoral angioplasty with or without stenting may suggest it is indicated only if autogenous vein is not available and prosthetic conduits such as polytetrafluorolene need to be considered.[109,110]

In contrast, most studies of endovascular intervention for tibial-level disease suggest that it may produce limb salvage results that are equivalent to those of bypass surgery.[111,112] A meta-analysis by Romiti and colleagues,[113] which compared the outcomes of 2,653 limbs in 2,557 patients who underwent angioplasty with the outcomes of 2,320 distal origin bypass grafts, demonstrated a limb salvage rate of 86.0% at 1 year, not significantly different than the 88.5% rate seen with distal origin bypass grafts. Similarly, an excellent single center study that used propensity scoring to match 418 patients undergoing infrapopliteal angioplasty and infrapopliteal bypass surgery for CLI demonstrated limb salvage rates that were equivalent at 1 year (85.5% vs 82.2%, respectively) and at 5 years (75.3% vs 76.0%, respectively).

The need for reintervention occurs at least as frequently after an index endovascular treatment as it does after infrainguinal bypass. Of the BASIL trial participants who were randomized and then had endovascular treatment, 21% underwent subsequent endovascular or surgical intervention. Single-center case series of infrainguinal and/or infrapopliteal angioplasty with or without stenting report reintervention rates that range from 26% to 37%.[99,103-107] So, using the patient survival and limb salvage rates described above and assuming a conservative reintervention rate of 26%, the actual proportions of patients in various clinical states 1 year after an index endovascular intervention would be: 13.0% dead, 12.2% alive with a major amputation, 19.6% alive with endovascular reintervention, and 55.2% alive without reintervention.

Functional outcomes, discharge disposition and quality of life after endovascular intervention for CLI

In contrast to the wealth of literature on patency and limb salvage, only a single publication described the effect of endovascular intervention on functional outcomes and discharge disposition.[66] This publication, describing a cohort of 841 CLI patients who underwent open or endovascular revascularization, reported an 86% overall rate of maintenance of ambulatory ability at 1 year and 81% at 2 years. Similarly, independent living status was maintained in 91% of all patients at 1 year and 88% at 2 years, with some small degree of further loss over time. Although separate rates for the open and endovascular subgroups were not reported, a multivariate analysis by these authors suggested that the type of revascularization was not an important determining factor for either postintervention ambulatory ability or independent living status.[66]

Quality of life after surgical and endovascular revascularization has been described using many global[114-116] and disease-focused[61] 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 Tangelder[45] (the results of which were further clarified in the rectification by Busschbach[46]). Patients in this study with a patent bypass graft had a mean EQ-5D$_{index}$ 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$_{index}$ 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.[22]

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 infrainguinal 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 infrainguinal bypass for ischemic ulcers[126]) and because they appear to adversely influence limb salvage, ambulatory function, and ability to live independently.[125]

Among 334 patients described by Chung and colleagues[71] that underwent infrainguinal 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.[71] Nearly identical results are reported by the University of Arizona Health Sciences Center group.[126] If one assumes that wound healing will continue at the constant rate described in the 1-year results by Chung and colleagues,[71] 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.[100,112,127-130] 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.[131] These rates appear comparable to the 40% wound healing rate at 10 months seen in the series of tibial angioplasty by Fernandez and coworkers.[100] 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,[132] when the extent of dry necrosis is thought to preclude limb salvage,[98,133] when conduit for bypass is limited or unavailable,[134] and when there is an inadequate distal target or outflow for bypass.[105,135] Furthermore, when a patient is nonambulatory at baseline, postoperative ambulation is unlikely; this too is sometimes used as a contraindication to limb salvage attempts.[20,45,66,70] 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.[64,132] The perioperative mortality associated with major lower extremity amputation has been reported to be 7% to 11%.[21,132] Although this is clearly higher than the perioperative mortality associated with infrainguinal 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 infrainguinal 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 infrainguinal 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.[136]

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

As outlined in a systematic review by Sansam and associates,[137] 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,[138] 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, 58% at 6 months, and 55% at 12 months. Beyond 1 year, the rate of decrease in the ability to walk slowed significantly, remaining at 51% at 2 years. The rates are comparable to those of other series (Table 1). Similar results were described by Nehler and coauthors:[21] among major 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]

It should be noted that most studies reporting ambulation after major amputation do not differentiate between below-knee (transtibial) and above-knee (transfemoral). At most centers, performance of a below-knee or above-knee amputation is based not only on soft tissue considerations and likelihood of healing, but also on a patient's preoperative functional status. So it might not be surprising to note that above-knee amputation has been associated with a lower likelihood of being fitted for a limb prosthesis and ability to ambulate after the operation;[138] this may reflect patient selection as much as the impact of the selection of amputation level. The study by McWhinnie and colleagues[142] may partly clarify the impact of level and preoperative function: among the 65 who could ambulate outdoors before below-knee amputation, only 54% could ambulate afterward, and of those who could ambulate indoors with assistance before below-knee amputation, only 41% could ambulate afterward. (For comparison, only 28% of patients who used a wheelchair most or all of the time achieved ambulatory ability with a limb prosthesis after a below-knee amputation). Relative to the literature on bypass outcomes, the literature on the outcomes of major amputation is sparse, limited by patient heterogeneity and differences in the definitions of various levels of function ("good" versus "poor" function with a limb prosthesis, for example[142]). However, for the purposes of a cost-effectiveness study, we suggest that the proportion of CLI patients ambulating after major amputation should be estimated at 52%, with a relatively wide distribution.

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%.[21] 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

First author	Alive at follow-up, n	Percent ambulatory
Taylor[138]	553	55
Nehler[21]	154	49
Remes[141]	119	33
Hermodsson[140]	112	63
McWhinnie[142]	100	41
Peng[139]	38	15
Total/overall percentage	1,015	52

Quality of life after major amputation in CLI patients

As part of the United Kingdom Prospective Diabetes Study (UKPDS 62), Clarke and colleagues[14] used the EuroQol EQ-5D on 3,667 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.[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.[143,144]

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.[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.[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,[146-150] and the high prevalence of survival-limiting comorbidities should be considered when weighing the risks and benefits of various management strategies.[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,[63] 84.4% at 1 year in the PREVENT III trial,[61] and 46% at 5 years in the BASIL trial.[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 infrainguinal 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[153-157] and have worked to establish many consensus guidelines for patient care.[158-162] Many have also become leaders in the recent patient safety, quality, and patient-oriented outcomes movement in medicine.[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[50]; in other words, optimizing the "value" of health care interventions we provide to our patients.[15] 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.[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.[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.[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 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 from other US centers would help greatly in informing clinicians in the means to optimize the cost-effectiveness and value of the services provided to patients.

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

The Brigham and Women's Hospital, Division of Vascular and Endovascular Surgery, Department of Surgery (Boston, MA): Neal R Barshes, MD, MPH, Michael Belkin, MD, C Keith Ozaki, MD, Louis L Nguyen, MD, MPH, MBA, Matthew T Menard, MD, James T McPhee, MD, Marcus E Semel, MD, MPH

The Center for the Evaluation of Value and Risk in Health, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center (Boston, MA): James Chambers, MPharm, MSc, Peter Neumann, ScD, Pei Jeng Lin, PhD, Joshua T Cohen, PhD

Baylor College of Medicine, Division of Vascular and Endovascular Therapy, Department of Surgery (Houston, TX): Pangiotis Kougias, MD

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

REFERENCES

1. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45 (Suppl S):S5–67.
2. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997;26:517–538.
3. Marston WA, Davies SW, Armstrong B, et al. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. J Vasc Surg 2006;44:108–114.
4. Norgren L, Alwmark A, Angqvist KA, et al. A stable prostacyclin analogue (iloprost) in the treatment of ischaemic ulcers of the lower limb. A Scandinavian-Polish placebo controlled, randomised multicenter study. Eur J Vasc Surg 1990;4:463–467.
5. Gordois A, Scuffham P, Shearer A, et al. The health care costs of diabetic peripheral neuropathy in the US. Diabetes Care 2003;26:1790–1795.
6. Dietzek AM, Gupta SK, Kram HB, et al. Limb loss with patent infra-inguinal bypasses. Eur J Vasc Surg 1990;4:413–417.
7. Age-adjusted hospital discharge rates for nontraumatic lower extremity amputation per 1,000 diabetic population by level. 2010. Available at: http://www.cdc.gov/diabetes/statistics/lealevel/fig8.htm. Accessed July 22, 2011.
8. 2009 National Population Projections: Summary Tables. Available at: http://www.census.gov/population/www/projections/2009cnmsSumTabs.html. Accessed July 22, 2011.
9. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. Circulation 2004;110:738–743.
10. Number of Persons with Diagnosed Diabetes, United States, 1983-2007. Available at: http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm. Accessed July 22, 2011.
11. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053.

12. Lavery LA, Peters EJ, Williams JR, et al. Reevaluating the way we classify the diabetic foot: restructuring the diabetic foot risk classification system of the International Working Group on the Diabetic Foot. Diabetes Care 2008;31:154–156.
13. Ramsey SD, Newton K, Blough D, et al. Patient-level estimates of the cost of complications in diabetes in a managed-care population. Pharmacoeconomics 1999;16:285–295.
14. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making 2002;22:340–349.
15. Porter M, Teisberg E. Redefining Health Care: Creating Value-Based Competition on Results. Boston: Harvard Business Press; 2006.
16. Neumann PJ, Rosen AB, Weinstein MC. Medicare and cost-effectiveness analysis. N Engl J Med 2005;353:1516–1522.
17. Eddy D. Reflections on science, judgment, and value in evidence-based decision making: a conversation with David Eddy by Sean R. Tunis. Health Aff (Millwood) 2007;26: w500–515.
18. Tunis SR, Pearson SD. US moves to improve health decisions. BMJ 2010;341:c3615.
19. Chambers JD, Neumann PJ, Buxton MJ. Does Medicare have an implicit cost-effectiveness threshold? Med Decis Making 2010;30:E14–27.
20. Goodney PP, Likosky DS, Cronenwett JL. Predicting ambulation status one year after lower extremity bypass. J Vasc Surg 2009;49:1431–1439 e1.
21. Nehler MR, Coll JR, Hiatt WR, et al. Functional outcome in a contemporary series of major lower extremity amputations. J Vasc Surg 2003;38:7–14.
22. Forbes JF, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Health-related quality of life outcomes, resource utilization, and cost-effectiveness analysis. J Vasc Surg 2010;51:43S–51S.
23. Werneck CC, Lindsay TF. Tibial angioplasty for limb salvage in high-risk patients and cost analysis. Ann Vasc Surg 2009;23: 554–559.
24. Zhang Z, Kolm P, Boden WE, et al. The cost-effectiveness of percutaneous coronary intervention as a function of angina severity in patients with stable angina. Circ Cardiovasc Qual Outcomes 2011;4:172–182.
25. Aasa M, Henriksson M, Dellborg M, et al. Cost and health outcome of primary percutaneous coronary intervention versus thrombolysis in acute ST-segment elevation myocardial infarction-Results of the Swedish Early Decision reperfusion Study (SWEDES) trial. Am Heart J 2010;160:322–328.
26. Mahoney EM, Mehta S, Yuan Y, et al. Long-term cost-effectiveness of early and sustained clopidogrel therapy for up to 1 year in patients undergoing percutaneous coronary intervention after presenting with acute coronary syndromes without ST-segment elevation. Am Heart J 2006;151:219–227.
27. Bakhai A, Stone GW, Mahoney E, et al. Cost effectiveness of paclitaxel-eluting stents for patients undergoing percutaneous coronary revascularization: results from the TAXUS-IV Trial. J Am Coll Cardiol 2006;48:253–261.
28. Capomolla S, Febo O, Ceresa M, et al. Cost/utility ratio in chronic heart failure: comparison between heart failure management program delivered by day-hospital and usual care. J Am Coll Cardiol 2002;40:1259–1266.
29. Linde C, Mealing S, Hawkins N, et al. Cost-effectiveness of cardiac resynchronization therapy in patients with asymptomatic to mild heart failure: insights from the European cohort of the REVERSE (Resynchronization Reverses remodeling in Systolic Left Ventricular Dysfunction). Eur Heart J 2010;32: 1632–1639.
30. Klersy C, De Silvestri A, Gabutti G, et al. Economic impact of remote patient monitoring: an integrated economic model derived from a meta-analysis of randomized controlled trials in heart failure. Eur J Heart Fail 2011;13:450–459.
31. Grosso AM, Bodalia PN, Macallister RJ, et al. Comparative clinical- and cost-effectiveness of candesartan and losartan in the management of hypertension and heart failure: a systematic review, meta- and cost-utility analysis. Int J Clin Pract 2011; 65:253–263.
32. Buxton M, Caine N, Chase D, et al. A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost-utility for these groups in a UK context. Health Technol Assess 2006;10:iii–iv, ix–xi, 1–164.
33. Hunink MG, Wong JB, Donaldson MC, et al. Revascularization for femoropopliteal disease. A decision and cost-effectiveness analysis. JAMA 1995;274:165–171.
34. Brothers TE, Rios GA, Robison JG, et al. Justification of intervention for limb-threatening ischemia: a surgical decision analysis. Cardiovasc Surg 1999;7:62–69.
35. Sanders LJ, Robbins JM, Edmonds ME. History of the team approach to amputation prevention: pioneers and milestones. J Vasc Surg 2010;52:3S–16S.
36. Rogers LC, Andros G, Caporusso J, et al. Toe and flow: essential components and structure of the amputation prevention team. J Vasc Surg 2010;52:23S–27S.
37. Stevens J, Franks PJ, Harrington M. A community/hospital leg ulcer service. J Wound Care 1997;6:62–68.
38. Muhs BE, Maldonado T, Crotty K, et al. Different endovascular referral patterns are being learned in medical and surgical residency training programs. Ann Vasc Surg 2006;20:217–222.
39. Mills JL, Beckett WC, Taylor SM. The diabetic foot: consequences of delayed treatment and referral. South Med J 1991; 84:970–974.
40. Hunink M, Glasziou P. Decision Making In Health and Medicine: Integrating Evidence and Values. New York: Cambridge University Press; 2009.
41. Eklund AE, Eriksson G, Olsson AG. A controlled study showing significant short term effect of prostaglandin E1 in healing of ischaemic ulcers of the lower limb in man. Prostaglandins Leukot Med 1982;8:265–271.
42. Ghanassia E, Villon L, Thuan Dit Dieudonne JF, et al. Long-term outcome and disability of diabetic patients hospitalized for diabetic foot ulcers: a 6.5-year follow-up study. Diabetes Care 2008;31:1288–1292.
43. Nikol S, Baumgartner I, Van Belle E, et al. Therapeutic angiogenesis with intramuscular NV1FGF improves amputation-free survival in patients with critical limb ischemia. Mol Ther 2008;16:972–978.
44. Quality of life in type 2 diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control (UKPDS 37). U.K. Prospective Diabetes Study Group. Diabetes Care 1999;22:1125–1136.
45. Tangelder MJ, McDonnel J, Van Busschbach JJ, et al. Quality of life after infrainguinal bypass grafting surgery. Dutch Bypass Oral Anticoagulants or Aspirin (BOA) Study Group. J Vasc Surg 1999;29:913–919.

46. Busschbach JJ, McDonnell J, Tangelder MJ, et al. EuroQol values for economic modeling quality of life after infrainguinal bypass grafting surgery: a rectification. J Vasc Surg 1999;30:1162–1163.
47. Davies AH, Hawdon AJ, Sydes MR, et al. Is duplex surveillance of value after leg vein bypass grafting? Principal results of the Vein Graft Surveillance Randomised Trial (VGST). Circulation 2005;112:1985–1991.
48. Chetter IC, Spark JI, Dolan P, et al. Quality of life analysis in patients with lower limb ischaemia: suggestions for European standardisation. Eur J Vasc Endovasc Surg 1997;13:597–604.
49. Ragnarson Tennvall G, Apelqvist J. Health-related quality of life in patients with diabetes mellitus and foot ulcers. J Diabetes Complications 2000;14:235–241.
50. Larsson B, Johannesson A, Andersson IH, et al. The Locomotor Capabilities Index; validity and reliability of the Swedish version in adults with lower limb amputation. Health Qual Life Outcomes 2009;7:44.
51. Redekop WK, Stolk EA, Kok E, et al. Diabetic foot ulcers and amputations: estimates of health utility for use in cost-effectiveness analyses of new treatments. Diabetes Metab 2004;30:549–556.
52. Sullivan SD, Lew DP, Devine EB, et al. Health state preference assessment in diabetic peripheral neuropathy. Pharmacoeconomics 2002;20:1079–1089.
53. Sprengers RW, Teraa M, Moll FL, et al. Quality of life in patients with no-option critical limb ischemia underlines the need for new effective treatment. J Vasc Surg 2010;52:843–849, 849 e1.
54. Van Hattum ES, Tangelder MJ, Lawson JA, et al. The long-term quality of life in patients with peripheral arterial disease after peripheral bypass surgery. J Am Coll Cardiol 2010;55:A156.E1458.
55. Ramsey SD, Newton K, Blough D, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes Care 1999;22:382–387.
56. Stockl K, Vanderplas A, Tafesse E, et al. Costs of lower-extremity ulcers among patients with diabetes. Diabetes Care 2004;27:2129–2134.
57. Harrington C, Zagari MJ, Corea J, et al. A cost analysis of diabetic lower-extremity ulcers. Diabetes Care 2000;23:1333–1338.
58. Wheelock FC Jr, Filtzer HS. Femoral grafts in diabetics. Resulting conservative amputations. Arch Surg 1969;99:776–780.
59. Pomposelli FB, Kansal N, Hamdan AD, et al. A decade of experience with dorsalis pedis artery bypass: analysis of outcome in more than 1000 cases. J Vasc Surg 2003;37:307–315.
60. Conte MS. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and the (hoped for) dawn of evidence-based treatment for advanced limb ischemia. J Vasc Surg 2010;51:69S–75S.
61. Conte MS, Bandyk DF, Clowes AW, et al. Results of PREVENT III: a multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery. J Vasc Surg 2006;43:742–751; discussion 751.
62. Brass EP, Anthony R, Dormandy J, et al. Parenteral therapy with lipo-ecraprost, a lipid-based formulation of a PGE1 analog, does not alter six-month outcomes in patients with critical leg ischemia. J Vasc Surg 2006;43:752–759.
63. Nehler MR, Brass EP, Anthony R, et al. Adjunctive parenteral therapy with lipo-ecraprost, a prostaglandin E1 analog, in patients with critical limb ischemia undergoing distal revascularization does not improve 6-month outcomes. J Vasc Surg 2007;45:953–960; discussion 960–961.
64. Bradbury AW, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. J Vasc Surg 2010;51:5S–17S.
65. Conte MS, Geraghty PJ, Bradbury AW, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. J Vasc Surg 2009;50:1462–1473 e1–3.
66. Taylor SM, Kalbaugh CA, Blackhurst DW, et al. Determinants of functional outcome after revascularization for critical limb ischemia: an analysis of 1000 consecutive vascular interventions. J Vasc Surg 2006;44:747–755; discussion 755–756.
67. Soderstrom MI, Arvela EM, Korhonen M, et al. Infrapopliteal percutaneous transluminal angioplasty versus bypass surgery as first-line strategies in critical leg ischemia: a propensity score analysis. Ann Surg 2010;252:765–773.
68. Abou-Zamzam AM Jr, Lee RW, Moneta GL, et al. Functional outcome after infrainguinal bypass for limb salvage. J Vasc Surg 1997;25:287–295; discussion 295–297.
69. Miller DK, Homan SM. Determining transition probabilities: confusion and suggestions. Med Decis Making 1994;14:52–58.
70. Gibbons GW, Burgess AM, Guadagnoli E, et al. Return to well-being and function after infrainguinal revascularization. J Vasc Surg 1995;21:35–44; discussion 44–45.
71. Chung J, Bartelson BB, Hiatt WR, et al. Wound healing and functional outcomes after infrainguinal bypass with reversed saphenous vein for critical limb ischemia. J Vasc Surg 2006;43:1183–1190.
72. Drummond MF, Sculpher MJ, Torrance GW, et al. Methods for the Economic Evaluation of Health Care Programmes. New York: Oxford University Press; 2005: 55–102.
73. Perler BA. Cost-efficacy issues in the treatment of peripheral vascular disease: primary amputation or revascularization for limb-threatening ischemia. J Vasc Interv Radiol 1995;6:111S–115S.
74. Auer AI, Hurley JJ, Binnington HB, et al. Distal tibial vein grafts for limb salvage. Arch Surg 1983;118:597–602.
75. Mackey WC, McCullough JL, Conlon TP, et al. The costs of surgery for limb-threatening ischemia. Surgery 1986;99:26–35.
76. Raviola CA, Nichter LS, Baker JD, et al. Cost of treating advanced leg ischemia. Bypass graft vs primary amputation. Arch Sur 1988;123:495–496.
77. Gupta SK, Veith FJ, Ascer E, et al. Cost factors in limb-threatening ischaemia due to infrainguinal arteriosclerosis. Eur J Vasc Surg 1988;2:151–154.
78. Cheshire NJ, Wolfe JH, Noone MA, et al. The economics of femorocrural reconstruction for critical leg ischemia with and without autologous vein. J Vasc Surg 1992;15:167–174; discussion 174–175.
79. Hunink MG, Cullen KA, Donaldson MC. Hospital costs of revascularization procedures for femoropopliteal arterial disease. J Vasc Surg 1994;19:632–641.
80. Johnson BF, Evans L, Drury R, et al. Surgery for limb threatening ischaemia: a reappraisal of the costs and benefits. Eur J Vasc Endovasc Surg 1995;9:181–188.

81. Singh S, Evans L, Datta D, et al. The costs of managing lower limb-threatening ischaemia. Eur J Vasc Endovasc Surg 1996; 12:359–362.
82. Eneroth M, Apelqvist J, Troeng T, et al. Operations, total hospital stay and costs of critical leg ischemia. A population-based longitudinal outcome study of 321 patients. Acta Orthop Scand 1996;67:459–465.
83. Luther M. Surgical treatment for chronic critical leg ischaemia: a 5 year follow-up of socioeconomic outcome. Eur J Vasc Endovasc Surg 1997;13:452–459.
84. Panayiotopoulos YP, Tyrrell MR, Arnold FJ, et al. Results and cost analysis of distal [crural/pedal] arterial revascularisation for limb salvage in diabetic and non-diabetic patients. Diabet Med 1997;14:214–220.
85. Jaff MR, Cahill KE, Yu AP, et al. Clinical outcomes and medical care costs among medicare beneficiaries receiving therapy for peripheralarterial disease. Ann Vasc Surg 2010;24:577–587.
86. Barnett PG. An improved set of standards for finding cost for cost-effectiveness analysis. Med Care 2009;47:S82–88.
87. Ross TK. Analyzing health care operations using ABC. J Health Care Finance 2004;30:1–20.
88. Azoulay A, Doris NM, Filion KB, et al. The use of the transition cost accounting system in health services research. Cost Eff Resour Alloc 2007;5:11.
89. Goodney PP, Beck AW, Nagle J, et al. National trends in lower extremity bypass surgery, endovascular interventions, and major amputations. J Vasc Surg 2009;50:54–60.
90. Kudo T, Chandra FA, Kwun WH, et al. Changing pattern of surgical revascularization for critical limb ischemia over 12 years: endovascular vs. open bypass surgery. J Vasc Surg 2006; 44:304–313.
91. Cull DL, Langan EM, Gray BH, et al. Open versus endovascular intervention for critical limb ischemia: a population-based study. J Am Coll Surg 2010;210:555–561, 561–563.
92. Conrad MF, Crawford RS, Hackney LA, et al. Endovascular management of patients with critical limb ischemia. J Vasc Surg 2011;53:1020–1025.
93. Faglia E, Dalla Paola L, Clerici G, et al. Peripheral angioplasty as the first-choice revascularization procedure in diabetic patients with critical limb ischemia: prospective study of 993 consecutive patients hospitalized and followed between 1999 and 2003. Eur J Vasc Endovasc Surg 2005;29:620–627.
94. Brosi P, Dick F, Do DD, et al. Revascularization for chronic critical lower limb ischemia in octogenarians is worthwhile. J Vasc Surg 2007;46:1198–1207.
95. Wolfe JH, Wyatt MG. Critical and subcritical ischaemia. Eur J Vasc Endovasc Surg 1997;13:578–582.
96. Adam DJ, Beard JD, Cleveland T, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet 2005;366:1925–1934.
97. Nguyen LL, Hevelone N, Rogers SO, et al. Disparity in outcomes of surgical revascularization for limb salvage: race and gender are synergistic determinants of vein graft failure and limb loss. Circulation 2009;119:123–130.
98. Carsten CG 3rd, Taylor SM, Langan EM 3rd, et al. Factors associated with limb loss despite a patent infrainguinal bypass graft. Am Surg 1998;64:33–37; discussion 37–38.
99. Robinson WP 3rd, Owens CD, Nguyen LL, et al. Inferior outcomes of autogenous infrainguinal bypass in Hispanics: an analysis of ethnicity, graft function, and limb salvage. J Vasc Surg 2009;49:1416–1425.
100. Fernandez N, McEnaney R, Marone LK, et al. Predictors of failure and success of tibial interventions for critical limb ischemia. J Vasc Surg 2010;52:834–842.
101. Singh N, Sidawy AN, DeZee KJ, et al. Factors associated with early failure of infrainguinal lower extremity arterial bypass. J Vasc Surg 2008;47:556–561.
102. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. N Engl J Med 2006;354:1879–1888.
103. Krankenberg H, Schluter M, Steinkamp HJ, et al. Nitinol stent implantation versus percutaneous transluminal angioplasty in superficial femoral artery lesions up to 10 cm in length: the femoral artery stenting trial (FAST). Circulation 2007;116:285–292.
104. Ihnat DM, Mills JL Sr. Current assessment of endovascular therapy for infrainguinal arterial occlusive disease in patients with diabetes. J Vasc Surg 2010;52:92S–95S.
105. Dalman R. Expected outcome: Early results, life table patency, limb salvage. In: Sr. JM, ed. Management of Chronic Lower Limb Ischemia. London: Arnold Publishers; 2000:106–112.
106. Klinkert P, Schepers A, Burger DH, et al. Vein versus polytetrafluoroethylene in above-knee femoropopliteal bypass grafting: five-year results of a randomized controlled trial. J Vasc Surg 2003;37:149–155.
107. Ballotta E, Renon L, Toffano M, et al. Prospective randomized study on bilateral above-knee femoropopliteal revascularization: Polytetrafluoroethylene graft versus reversed saphenous vein. J Vasc Surg 2003;38:1051–1055.
108. Korhonen M, Biancari F, Soderstrom M, et al. Femoropopliteal balloon angioplasty vs. bypass surgery for CLI: a propensity score analysis. Eur J Vasc Endovasc Surg 2011;41:378–384.
109. Dosluoglu HH, Cherr GS, Lall P, et al. Stenting vs above knee polytetrafluoroethylene bypass for TransAtlantic Inter-Society Consensus-II C and D superficial femoral artery disease. J Vasc Surg 2008;48:1166–1174.
110. Shah PS, Hingorani A, Ascher E, et al. Full metal jacket stenting of the superficial femoral artery: a retrospective review. Ann Vasc Surg 2011;25:127–131.
111. Conrad MF, Kang J, Cambria RP, et al. Infrapopliteal balloon angioplasty for the treatment of chronic occlusive disease. J Vasc Surg 2009;50:799–805 e4.
112. Dosluoglu HH, Cherr GS, Lall P, et al. Peroneal artery-only runoff following endovascular revascularizations is effective for limb salvage in patients with tissue loss. J Vasc Surg 2008;48: 137–143.
113. Romiti M, Albers M, Brochado-Neto FC, et al. Meta-analysis of infrapopliteal angioplasty for chronic critical limb ischemia. J Vasc Surg 2008;47:975–981.
114. Valensi P, Girod I, Baron F, et al. Quality of life and clinical correlates in patients with diabetic foot ulcers. Diabetes Metab 2005;31:263–271.
115. Engelhardt M, Bruijnen H, Scharmer C, et al. Improvement of quality of life six months after infrageniculate bypass surgery: diabetic patients benefit less than non-diabetic patients. Eur J Vasc Endovasc Surg 2006;32:182–187.
116. Brothers TE, Robison JG, Elliott BM. Prospective decision analysis for peripheral vascular disease predicts future quality of life. J Vasc Surg 2007;46:701–708; discussion 708.
117. Ballard JL, Eke CC, Bunt TJ, et al. A prospective evaluation of transcutaneous oxygen measurements in the management of

diabetic foot problems. J Vasc Surg 1995;22:485–490; discussion 490–492.
118. de Graaff JC, Ubbink DT, Legemate DA, et al. Evaluation of toe pressure and transcutaneous oxygen measurements in management of chronic critical leg ischemia: a diagnostic randomized clinical trial. J Vasc Surg 2003;38:528–534.
119. Ubbink DT, Spincemaille GH, Reneman RS, et al. Prediction of imminent amputation in patients with non-reconstructible leg ischemia by means of microcirculatory investigations. J Vasc Surg 1999;30:114–121.
120. Bunt TJ, Holloway GA. TcPO2 as an accurate predictor of therapy in limb salvage. Ann Vasc Surg 1996;10:224–227.
121. Faglia E, Clerici G, Caminiti M, et al. Predictive values of transcutaneous oxygen tension for above-the-ankle amputation in diabetic patients with critical limb ischemia. Eur J Vasc Endovasc Surg 2007;33:731–736.
122. Simons JP, Goodney PP, Nolan BW, et al. Failure to achieve clinical improvement despite graft patency in patients undergoing infrainguinal lower extremity bypass for critical limb ischemia. J Vasc Surg 2010;51:1419–1424.
123. Nehler MR, Hiatt WR, Taylor LM Jr. Is revascularization and limb salvage always the best treatment for critical limb ischemia? J Vasc Surg 2003;37:704–708.
124. Taylor SM. Current status of heroic limb salvage for critical limb ischemia. Am Surg 2008;74:275–284.
125. Taylor SM, Johnson BL, Samies NL, et al. Contemporary management of diabetic neuropathic foot ulceration: a study of 917 consecutively treated limbs. J Am Coll Surg 2011;212: 532–545.
126. Goshima KR, Mills JL Sr, Hughes JD. A new look at outcomes after infrainguinal bypass surgery: traditional reporting standards systematically underestimate the expenditure of effort required to attain limb salvage. J Vasc Surg 2004;39:330–335.
127. Pardo M, Alcaraz M, Ramon Breijo F, et al. Increased transcutaneous oxygen pressure is an indicator of revascularization after peripheral transluminal angioplasty. Acta Radiol 2010; 51:990–993.
128. Clair DG, Dayal R, Faries PL, et al. Tibial angioplasty as an alternative strategy in patients with limb–threatening ischemia. Ann Vasc Surg 2005;19:63–68.
129. Matsushita M, Ikezawa T, Banno H. Relationship between the diameter of the vein graft and postoperative ankle brachial pressure index following femoro–popliteal bypass. Int Angiol 2008;27:329–332.
130. Abou-Zamzam AM Jr, Moneta GL, Lee RW, et al. Peroneal bypass is equivalent to inframalleolar bypass for ischemic pedal gangrene. Arch Surg 1996;131:894–898; discussion 898–899.
131. Neville R, Steinberg J, Babrowicz J, et al. A comparison of endovascular revascularization and bypass in regards to healing rates of ischemic wounds. J Vasc Surg 2010;51:11S–12S.
132. Abou-Zamzam AM Jr, Teruya TH, Killeen JD, et al. Major lower extremity amputation in an academic vascular center. Ann Vasc Surg 2003;17:86–90.
133. Berceli SA, Chan AK, Pomposelli FB Jr, et al. Efficacy of dorsal pedal artery bypass in limb salvage for ischemic heel ulcers. J Vasc Surg 1999;30:499–508.
134. Schanzer A, Hevelone N, Owens CD, et al. Technical factors affecting autogenous vein graft failure: observations from a large multicenter trial. J Vasc Surg 2007;46:1180–1190; discussion 1190.
135. O'Mara CS, Flinn WR, Neiman HL, et al. Correlation of foot arterial anatomy with early tibial bypass patency. Surgery 1981; 89:743–752.
136. Barshes NR, Menard MT, Nguyen LL, et al. Infrainguinal bypass is associated with lower perioperative mortality than major amputation in high–risk surgical candidates. J Vasc Surg 2011;53:1251–1259.
137. Sansam K, Neumann V, O'Connor R, et al. Predicting walking ability following lower limb amputation: a systematic review of the literature. J Rehabil Med 2009;41:593–603.
138. Taylor SM, Kalbaugh CA, Blackhurst DW, et al. Preoperative clinical factors predict postoperative functional outcomes after major lower limb amputation: an analysis of 553 consecutive patients. J Vasc Surg 2005;42:227–235.
139. Peng CW, Tan SG. Perioperative and rehabilitative outcomes after amputation for ischaemic leg gangrene. Ann Acad Med Singapore 2000;29:168–172.
140. Hermodsson Y, Ekdahl C, Persson BM. Outcome after transtibial amputation for vascular disease. A follow-up after eight years. Scand J Caring Sci 1998;12:73–80.
141. Remes L, Isoaho R, Vahlberg T, et al. Predictors for institutionalization and prosthetic ambulation after major lower extremity amputation during an eight-year follow-up. Aging Clin Exp Res 2009;21:129–135.
142. McWhinnie DL, Gordon AC, Collin J, et al. Rehabilitation outcome 5 years after 100 lower-limb amputations. Br J Surg 1994;81:1596–1599.
143. Kaambwa B, Bryan S, Barton P, et al. Costs and health outcomes of intermediate care: results from five UK case study sites. Health Soc Care Community 2008;16:573–581.
144. Cunliffe AL, Gladman JR, Husbands SL, et al. Sooner and healthier: a randomised controlled trial and interview study of an early discharge rehabilitation service for older people. Age Ageing 2004;33:246–252.
145. MacKenzie EJ, Jones AS, Bosse MJ, et al. Health-care costs associated with amputation or reconstruction of a limb-threatening injury. J Bone Joint Surg Am 2007;89:1685–1692.
146. Criqui MH, McClelland RL, McDermott MM, et al. The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2010;56:1506–1512.
147. Weatherley BD, Nelson JJ, Heiss G, et al. The association of the ankle-brachial index with incident coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study, 1987-2001. BMC Cardiovasc Disord 2007;7:3.
148. Wild SH, Byrne CD, Smith FB, et al. Low ankle-brachial pressure index predicts increased risk of cardiovascular disease independent of the metabolic syndrome and conventional cardiovascular risk factors in the Edinburgh Artery Study. Diabetes Care 2006;29:637–642.
149. Lee AJ, Price JF, Russell MJ, et al. Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: the Edinburgh Artery Study. Circulation 2004;110:3075–3080.
150. Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008;300: 197–208.
151. Bradbury AW, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: A survival prediction model to facilitate clinical decision making. J Vasc Surg 2010;51:52S–68S.

152. Bradbury AW, Adam DJ, Bell J, et al. Multicentre randomised controlled trial of the clinical and cost–effectiveness of a bypass–surgery–first versus a balloon–angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial. Health Technol Assess 2010; 14:1–210, iii–iv.
153. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991;325:445–453.
154. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995;273:1421–1428.
155. Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493–1501.
156. Lederle FA, Freischlag JA, Kyriakides TC, et al. Outcomes following endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. JAMA 2009;302:1535–1542.
157. Cooper CJ, Murphy TP, Matsumoto A, et al. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: rationale and design of the CORAL trial. Am Heart J 2006;152:59–66.
158. Hobson RW 2nd, Mackey WC, Ascher E, et al. Management of atherosclerotic carotid artery disease: clinical practice guidelines of the Society for Vascular Surgery. J Vasc Surg 2008;48: 480–486.
159. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Circulation 2011 May 25. [Epub ahead of print]
160. Lee WA, Matsumura JS, Mitchell RS, et al. Endovascular repair of traumatic thoracic aortic injury: clinical practice guidelines of the Society for Vascular Surgery. J Vasc Surg 2011;53: 187–192.
161. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Catheter Cardiovasc Interv 2010;76:E43–86.
162. Chaikof EL, Brewster DC, Dalman RL, et al. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. J Vasc Surg 2009;50: S2–49.
163. Owens DK, Qaseem A, Chou R, et al. High-value, cost-conscious health care: concepts for clinicians to evaluate the benefits, harms, and costs of medical interventions. Ann Intern Med 2011;154:174–180.
164. Briggs A, Claxton K, Schulpher M. Decision Modelling for Health Economic Evaluation. New York: Oxford University Press; 2006.
165. Congressional Budget Office (2007). Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role. (CBO Publication 8891). Washington, DC: US Government Printing Office. Available at: http://www.cbo.gov/ftpdocs/88xx/doc8891/12-18-ComparativeEffectiveness.pdf. Last accessed August 9, 2011.

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)[1] 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 Transfection III (PREVENT III)[2], 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 a*mputation 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 (alive and dead, amputation or not). 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[9] 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** = [(*2° patency – 1° 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 prosthetic, 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.

*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 al[23] has not been incorporated into the current study.

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 ischemia[10,16,17], 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 Index[19] and the EuroQol[20], 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 limitations[21], it is generally regarded as single best measure of health that can be used across disease states.[7,22] 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]

Appendix 3. Recommended Baseline Values and Distributions for Parameters Important to the Modeling of Outcomes of Managing Rutherford Category 5 Critical Limb Ischemia

Clinical parameters	Baseline value	Recommended distribution	Source
Events affecting all patients			
Baseline annual mortality rate	0.117	Beta (80.5, 607.6)	Conte[23]
Events after surgical revascularization			
Additional periprocedural mortality, surgical revascularization	0.026	Beta (18, 679)	Conte[2]
Limb salvage at one year following surgical revascularization	0.892	Beta (620, 87)	Conte[2]
Probability of remaining alive but requiring major amputation by the end of the first year after surgical revascularization	1-limb salvage		See review text
Probability of remaining alive but requiring major amputation beyond the first year after surgical revascularization	0.026		See review text
Probability of remaining ambulatory	0.971	Beta (402, 12)	Abou-Zamzam[24]
Probability of maintenance of independent living	0.986	Beta (412, 4)	Abou-Zamzam[24]
Probability of initial discharge to intermediate care facility	0.287	Beta (371, 963)	Goodney[25]
Probability of wound healing during one year	1.00		See review text
Events after endovascular revascularization			
Additional periprocedural mortality, endovascular revascularization	0.026	Beta (18, 679)	Equal to operative mortality per BASIL trial[26]
Probability of remaining alive but requiring major amputation by the end of the first year after endovascular revascularization	0.122	Beta (17.8, 128.1)	See review text
Probability of remaining alive but requiring major amputation by the end of the subsequent year after surgical revascularization	0.026		See review text
Probability of requiring revision/reintervention after endovascular revascularization	0.260	Beta (319, 1085)	See review text
Probability of requiring revision/reintervention after surgical revascularization	0.227	Beta (319, 1085)	Berceli[9]
Events after major amputation			
Additional periprocedural mortality, major amputation	1.52x operative mortality		See review text
Events after local wound care			
Annual probability of major amputation with local wound care alone	0.380	Beta (33, 55)	See review text
Annual probability of ulcer/wound healing with local wound care alone	0.410	Beta (14, 21)	
Annual probability of recurrence after ulcer/wound healing with local wound care alone	0.610	Beta (42, 27)	
Utilities			
Utility after amputation	0.54	Triangular (0.28, 0.52)	
Utility after intact limb with healed wound	0.62	Beta (221, 136)	Forbes,[27] review text
Utility after with intact limb and open wound	0.42	Triangular (0.28, 0.52)	See review text
Utility with spontaneous healing of a foot wound (ie, local wound care alone)	0.64	Beta (223, 126)	Forbes,[27] review text
Utility of death	0.0		By convention

Appendix 4. Common Procedural Terminology Used to Identify and Categorize Interventions Done for Critical Limb Ischemia

Procedure	CPT codes
Surgical revascularization	
Femoropopliteal bypass with vein, prosthetic conduit, or in-situ	35556, 35656, or 35583
Femorotibial bypass with vein, prosthetic conduit, or in-situ	35566, 35666, or 35585
Distal origin grafts with vein, prosthetic conduits, or in-situ	35570, 35571, 35671, or 35587
Endovascular revascularization	
Femoropopliteal or tibial vessel balloon angioplasty	35470 and 35474
Femoropopliteal or tibial vessel percutaneous atherectomy	35493 and 35495
Femoropopliteal or tibial vessel stent placement	37205 and 37206
Surgical revision of threatened / failing bypass grafts	
Thrombectomy of arterial non-dialysis graft	35875 and 35876
Open revision of femoral anastomosis of a synthetic arterial bypass graft	35883 and 35884
Endovascular revision of threatened / failing bypass grafts*	
Percutaneous arterial thrombectomy	37184, 37185 and 37186
Femoropopliteal or tibial vessel balloon angioplasty	35470 and 35474
Femoropopliteal or tibial vessel percutaneous atherectomy	35493 and 35495
Femoropopliteal or tibial vessel stent placement	37205 and 37206
Diagnostic angiogram	
Cannulation of aortic/pelvic/lower extremity arterial branches	36245, 36246, 36247
Major amputations	
Above-knee amputation	27590 and 27592
Below-knee amputation	27880 and 27882
Minor amputations	
Toe amputation	28825 and 28820
Mid-foot amputation	28810
Incision and drainage, simple or complex	10060 and 10061
Split-thickness skin grafts <100 cm^2	15100
Debridement below fascia	28003

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

1. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45 Suppl S:S5–67.
2. Conte MS, Bandyk DF, Clowes AW, et al. Results of PREVENT III: a multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery. J Vasc Surg 2006;43(4):742–751; discussion 751.
3. Brass EP, Anthony R, Dormandy J, et al. Parenteral therapy with lipo-ecraprost, a lipid-based formulation of a PGE1 analog, does not alter six-month outcomes in patients with critical leg ischemia. J Vasc Surg 2006;43(4):752–9.
4. Nehler MR, Brass EP, Anthony R, et al. Adjunctive parenteral therapy with lipo-ecraprost, a prostaglandin E1 analog, in patients with critical limb ischemia undergoing distal revascularization does not improve 6-month outcomes. J Vasc Surg 2007; 45(5):953–60; discussion 960-1.
5. Bradbury AW, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. J Vasc Surg 2010;51(5 Suppl):5S–17S.
6. Oxford Centre for Evidence-Based Medicine Levels of Evidence. Available at: www.cebm.net. Accessed January 18th, 2010.
7. Briggs A, Claxton K, Schulpher M. Decision modelling for health economic evaluation. New York: Oxford University Press, 2006.
8. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997;26(3):517–38.
9. Berceli SA, Hevelone ND, Lipsitz SR, et al. Surgical and endovascular revision of infrainguinal vein bypass grafts: analysis of midterm outcomes from the PREVENT III trial. J Vasc Surg 2007;46(6):1173–1179.
10. Morgan MB, Crayford T, Murrin B, et al. Developing the Vascular Quality of Life Questionnaire: a new disease-specific quality of life measure for use in lower limb ischemia. J Vasc Surg 2001;33(4):679–87.
11. Gibbons GW, Burgess AM, Guadagnoli E, et al. Return to well-being and function after infrainguinal revascularization. J Vasc Surg 1995;21(1):35–44; discussion 44-5.
12. Chung J, Bartelson BB, Hiatt WR, et al. Wound healing and functional outcomes after infrainguinal bypass with reversed

saphenous vein for critical limb ischemia. J Vasc Surg 2006;43(6):1183–90.
13. Nguyen LL, Lipsitz SR, Bandyk DF, et al. Resource utilization in the treatment of critical limb ischemia: The effect of tissue loss, comorbidities, and graft-related events. J Vasc Surg 2006; 44(5):971–5; discussion 975–6.
14. Ragnarson Tennvall G, Apelqvist J. Health-related quality of life in patients with diabetes mellitus and foot ulcers. J Diabetes Complications 2000;14(5):235–41.
15. Redekop WK, Stolk EA, Kok E, et al. Diabetic foot ulcers and amputations: estimates of health utility for use in cost-effectiveness analyses of new treatments. Diabetes Metab 2004; 30(6):549–56.
16. Spertus J, Jones P, Poler S, et al. The peripheral artery questionnaire: a new disease-specific health status measure for patients with peripheral arterial disease. Am Heart J 2004;147(2):301–8.
17. Chong PF, Garratt AM, Golledge J, et al. The intermittent claudication questionnaire: a patient-assessed condition-specific health outcome measure. J Vasc Surg 2002;36(4):764–71; discussion 863–4.
18. Hunink M, Glasziou P. Decision making in health and medicine: Integrating evidence and values. New York: Cambridge University Press, 2009.
19. Torrance GW, Furlong W, Feeny D, et al. Multi-attribute preference functions. Health Utilities Index. Pharmacoeconomics 1995;7(6):503–20.
20. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35(11):1095–108.
21. Neumann PJ, Greenberg D. Is the United States ready for QALYs? Health Aff (Millwood) 2009;28(5):1366–71.
22. Drummond MF, Sculpher MJ, Torrance GW, et al. Methods for the Economic Evaluation of Health Care Programmes. New York: Oxford University Press; 2005:pp. 55–102.
23. Conte MS, Geraghty PJ, Bradbury AW, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. J Vasc Surg 2009;50(6):1462–73 e1-3.
24. Abou-Zamzam AM Jr, Lee RW, Moneta GL, et al. Functional outcome after infrainguinal bypass for limb salvage. J Vasc Surg 1997;25:287–295; discussion 295–297.
25. Goodney DP, Likosky DS, Cronenwett JL. Predicting ambulation status one year after lower extremity bypass. J Vasc Surg 2009;49:1431–9 e1.
26. Adam DJ, Beard JD, Cleveland T, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet 2005;366(9501):1925–34.
27. Forbes JF, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Health-related quality of life outcomes, resource utilization, and cost-effectiveness analysis. J Vasc Surg 2010;51(5 Suppl):43S–51S.