HHS Public Access

Author manuscript

Ann Vasc Surg. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Ann Vasc Surg. 2016 January ; 30: 82–92. doi:10.1016/j.avsg.2015.10.004.

Risk Factors for Long-Term Mortality and Amputation after Open and Endovascular Treatment of Acute Limb Ischemia

Elizabeth A Genovese, MD MS[a], **Rabih A Chaer, MD MSc**[a], **Ashraf G Taha, MD**[a,b], **Luke K Marone, MD**[a], **Efthymios Avgerinos, MD**[a], **Michel S Makaroun, MD**[a], and **Donald T Baril, MD**[a]

[a] Division of Vascular Surgery, Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA

[b] Department of Vascular Surgery, Assiut University, Assiut, Egypt

Abstract

Background—Acute limb ischemia (ALI) is a highly morbid and fatal vascular emergency with little known about contemporary, long-term patient outcomes. The goal was to determine predictors of long-term mortality and amputation following open and endovascular treatment of ALI.

Methods—A retrospective review of ALI patients at a single institution from 2005-2011 was performed to determine the impact of revascularization technique on 5-year mortality and amputation. For each main outcome two multivariable models were developed; the first adjusted for preoperative clinical presentation and procedure type, the second also adjusted for postoperative adverse events.

Results—Four hundred and forty-five limbs in 411 patients were treated for ALI. Interventions included surgical thrombectomy (48%), emergent bypass (18%), and endovascular revascularization (34%). Mean age was 68 ± 15 years, 54% were male, and 23% had cancer. The majority of patients presented with Rutherford Classification IIa (54%) or IIb (39%). The etiology of ALI included embolism (27%), in-situ thrombosis (28%), thrombosed bypass grafts (32%), and thrombosed stents (13%). Patients treated with open procedures had significantly more advanced ischemia and higher rates of post-operative respiratory failure, while patients undergoing endovascular interventions had higher rates of technical failure. Rates of post-procedural bleeding and cardiac events were similar between both treatments. Excluding Rutherford Class III patients (n=12), overall 5-year mortality was 54% (stratified by treatment, 65% for thrombectomy, 63% for bypass, and 36% for endovascular, p<.001); 5-year amputation was 28% (stratified by

Corresponding Author: Elizabeth A Genovese, MD MS, Division of Vascular Surgery, Heart and Vascular Institute, University of Pittsburgh Medical Center, A-1017 PUH; 200 Lothrop Street, Pittsburgh, PA 15213, Phone: 216-403-1811/ Fax: 412-291-1669, genovesee@upmc.edu.

Presented at the *Vascular and Endovascular Surgery Society* 2015 Annual Winter Meeting, Vail CO, January 2015, as an oral presentation

treatment, 18% for thrombectomy, 27% for bypass, and 17% for endovascular, p=0.042). Adjusting for comorbidities, patient presentation, adverse events and treatment method, the risk of mortality increased with age (HR=1.04, p<.001), female gender (HR=1.50, p=.031), cancer (HR=2.19, p<.001), fasciotomy (HR=1.69, p=.204) in-situ thrombosis or embolic etiology (HR=1.73, p=.007), cardiac adverse events (HR=2.25, p<.001), respiratory failure (HR=2.72, p<.001), renal failure (HR=4.70, p<.001) and hemorrhagic events (HR=2.25, p=.003). Risk of amputation increased with advanced ischemia (Rutherford IIb compared to IIa, HR=2.57, p<.001), thrombosed bypass etiology (HR=3.53,p=.002), open revascularization (HR=1.95,p=.022), and technical failure of primary intervention (HR=6.01, p<.001).

Conclusions—Following the treatment of ALI, long-term mortality and amputation rates were greater in patients treated with open techniques; OR patients presented with a higher number of comorbidities and advanced ischemia, while also experiencing a higher rate of major postoperative complications. Overall, mortality rates remained high and were most strongly associated with baseline comorbidities, acuity of presentation, and perioperative adverse events, particularly respiratory failure. Comparatively, amputation risk was most highly associated with advanced ischemia, thrombosed bypass, and failure of the initial revascularization procedure.

INTRODUCTION

Acute limb ischemia (ALI) is the sudden onset of decreased arterial perfusion with an imminent threat to limb viability.[1] This is a highly morbid condition with one-year mortality and amputation rates ranging between 16-42% and 11-37%, respectively.[2-5] Older reports estimate 5-year mortality to be as high as 33-83%.[6-8] ALI patients are extremely heterogeneous with numerous comorbidities and limited physiologic reserve. Compared to patients treated electively for peripheral arterial disease, ALI patients are not medically optimized and present with advanced disease states contributing to significantly higher post-operative complications, mortality and limb loss.[2,4,5,9,10]

Revascularization options for ALI patients include open revascularization (OR) and endovascular revascularization (ER). Given the reduced physiological stress of ER on frail ALI patients, there has been a dramatic increase in use and experience with ER over the past decade.[5,11] However, these less invasive procedures may require greater time to reestablish arterial flow and have historically been associated with higher rates of hemorrhagic complications, distal embolization, and lower rates of technical success compared to OR.[12-17]

Older studies have demonstrated similar short-term limb salvage and survival rates for ER and OR, despite the different adverse event profiles of each therapy.[11,13,1812,16,19] Moreover, there has been a paucity of information reported on the long-term outcomes of these patients. Given this, especially in the contemporary era with increased experience and usage of ER, our goal was to determine predictive risk factors of mortality and limb loss to better guide the choice of therapy and optimize long-term outcomes.

METHODS

This is a single institution, retrospective analysis of a prospectively collected database of all adult patients (≥18 years of age) who were treated by the Division of Vascular Surgery at the University of Pittsburgh Medical Center for lower extremity ALI from January 1, 2005 through May 31, 2011, with follow-up data collected through August 1, 2014. This study was approved by the Institutional Review Board of the University of Pittsburgh. No study specific consent was required as no patient identifiers were collected and the study received an exempt status. All patients gave informed consent to undergo the revascularization procedures.

Patient Selection

Lower extremity ALI was defined as the sudden onset or deterioration of arterial perfusion of one or both lower extremities causing a threat to limb viability from an arterial thromboembolism, in-situ thrombosis of the native vessels, or thrombosis of a previous bypass graft or stent.[1] Blue toe syndrome and ALI secondary to trauma, aortic dissection, or thrombosed aneurysms were excluded from the study. The severity of ALI was determined based on Rutherford Classification.[1]

Pre-Operative Data

Data was collected on demographics (age, gender, race), baseline comorbidities (coronary artery disease, congestive heart failure, atrial fibrillation, history of coronary artery bypass graft, chronic obstructive pulmonary disease, smoking status, cerebrovascular accident, caner, hypertension, hyperlipidemia, chronic renal insufficiency including hemodialysis, diabetes mellitus), pre-operative medications (warfarin, clopidogrel, aspirin, and statins), and previous vascular interventions. Pertinent clinical presentation information was also collected, including etiology of the ALI (embolism, in-situ arterial thrombosis, thrombosed vein or prosthetic bypass graft, thrombosed stent) and degree of ischemia at presentation (defined by Rutherford Classification).

Procedures

Patients underwent either ER or OR at the discretion of the treating vascular surgeon. Although there is no clear divisional protocol for ALI, patients with advanced ischemia were more likely to be treated with OR in an attempt to establish prompt reperfusion, whereas patients with less severe ischemia were more likely to undergo ER. Similar to the overall national trend of increasing use of ER,[5] during the early years of the study there was a preference for OR and over time there was an rising use of ER for initial treatment of ALI.[5] For ER procedures, technical success was achieved when in-line blood flow was restored to the foot (or to the ankle through a patent peroneal artery or large collateral vessel) with multiphasic Doppler signals without requirement for surgical conversion. Because many OR patients did not have completion angiograms, surgical intervention was considered technically successful when a palpable pulse or multiphasic Doppler signals were detected over at least one of the pedal vessels at the completion of the procedure. Patients were analyzed based on their index procedure type and subsequent treatment cross-overs were considered to be technical failures. ER included catheter directed thrombolysis,

pharmacomechanical thrombolysis, or a combination of both, as previously described.[18] OR included open thrombectomy, with or without endarterectomy, or arterial bypass with either vein or prosthetic grafts.

Follow-Up and Outcomes

The main long-term outcomes of interest were 5-year major amputation, mortality and cause of death. Peri-operative data collected included the need for lower leg four compartment fasciotomy, technical success of the initial revascularization procedure, subsequent re-interventions, and peri-operative adverse events (AEs) such as bleeding (requiring blood product transfusion or re-intervention), major cardiac events, renal failure requiring hemodialysis, or respiratory failure (defined as intubation >48 hours, re-intubation, or tracheostomy).

Statistical Analysis

In order to investigate baseline differences between patients who underwent OR to ER, patient demographics, incidence of pre-operative comorbidities, clinical presentation, and post-operative complications were compared between procedure types (open thrombectomy, emergent bypass, or ER) using Pearson Chi-Square or Fisher's Exact Test for categorical variables, and Analysis of Variance for continuous variables. The frequency of cause of death was described for procedure types when available.

A comparison of mortality and amputation rates at 5 years were performed using Kaplan-Meier analysis for patient demographics, co-morbidities, clinical presentation, procedure type (OR vs. ER), and peri-operative complications. Rutherford III patients were excluded from analysis as the majority of these patients (>90%) did not survive to 1 year. Two Cox-Proportional Hazards models were created to determine the impact of procedure type (OR vs. ER) on mortality and amputation rates at 5 years while controlling for the differences between the two cohorts. The first model included variables adjusting for clinical presentation alone, while the second model also adjusted for post-operative AEs to determine if procedure type continued to confer an impact on the outcome of interest after adjusting for AEs or if long-term outcomes were mediated through the post-operative course. Variables were entered into the multivariable model if their initial Kaplan Meier p-value was <0.15, excluding highly correlated variables (Pearson correlation <0.45, $p<0.05$).

RESULTS

A total of 411 patients presented with ALI effecting 445 limbs at our institution between January 1, 2005 and May 31, 2011. Treatment modalities included open thrombectomy (48%), emergent bypass (18%) and ER (34%). The average follow-up was 28.6 ± 28.3 months. The incidence of baseline patient characteristics and comorbidities of the entire cohort and for each treatment strategy are detailed in Table I. The majority of patients were male and Caucasian with a high prevalence of typical vascular comorbidities such as coronary artery disease, hypertension, hyperlipidemia, and diabetes. Patients who underwent open thrombectomy were significantly older with a higher prevalence of atrial fibrillation. Those requiring emergent bypass had a significantly higher incidence of COPD. In

comparison, patients who underwent ER had higher rates of smoking, clopidogrel and statin use, and lower rates of coumadin use. With regards to clinical presentation (Table II) patients who underwent a thrombectomy had significantly fewer prior vascular interventions and a higher rate of embolic etiology, while ER patients had a higher incidence of thrombosed stents. Patients who underwent OR had more advanced ischemia, with 48% presenting with Rutherford Class IIb ischemia, while 10% and 69% of ER patients had Class I and Class IIa, respectively. Table III describes major postoperative complication rates, which were similar between the three groups with the following exceptions; bypass patients had more wound infections and respiratory failure occurred more frequently in the OR patients. In comparison, there was a higher rate of technical failure in the ER group. Of note, there were no significant differences in rates of hemorrhagic complications or cardiac AEs between procedure types.

The overall mortality rate at 30 days, 1 year and 5 years was 9.3±1.5%, 26.3±2.3%, and 54.0±3.0%, respectively. Forty-one patients died during their initial hospitalization (10% overall, 12.8% of OR patients, 4.3% of ER patients, p=.008). The causes of death were investigated for all patients who were deceased (n=172). Seventeen percent of patients died from cancer, 16% had cardiovascular etiology,7% multisystem organ failure, 6% respiratory failure, 6% infection/sepsis, 5% neurologic events and 42% of patients the cause of death was unable to be identified. A meaningful statistical comparison of causes of death by procedure type could not be performed given the small number of patients in certain categories.

Univariable analysis, using Kaplan Meier time-to-event analysis, was performed to determine predictors of 5-year mortality investigating comorbidities, clinical presentation, procedure type, and post-operative AEs. Significant predictors (p<.05) included female gender, never smoking, coronary artery disease, congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease, cancer (Figure 1A), diabetes, pre-operative renal failure, no aspirin use, no clopidogrel use, etiology of embolic or in-situ thrombosis (Figure 1B), advanced ischemia at presentation, open revascularization compared to ER(Figure 1C), post-operative hemorrhage, cardiac AE, and respiratory failure (Figure 1D).

Two multivariable models were created to determine predictors of long-term mortality. The first model (Table IV) controlled for pre-operative variables only (i.e., demographics, comorbidities, clinical presentation) to determine the impact of procedure type on long-term mortality after adjusting for the differences between the ER and OR cohorts. Variables associated with an increased risk of mortality were age (HR: 1.04 per year), female gender (HR: 1.46), COPD (HR: 1.54), cancer (HR: 1.81), pre-operative renal failure (HR: 7.21), increasing severity of ischemia (HR: 3.88 and 4.80 for Class IIa and IIb, respectively, compared to Class I), fasciotomies (HR: 1.71), embolic or in-situ thrombosis etiology compared to thrombosed bypass or stent (HR: 1.54), and open revascularization (HR: 1.53).

We hypothesized that the post-operative course would also have a significant impact on mortality in the long-term period and univariable analysis demonstrated that some major AEs were associated with a drastic increase in mortality rates. A second model was therefore created controlling for patient baseline severity of illness, clinical presentation, and

procedure type, with the addition of major post-operative AEs (see Table V). Age, gender, cancer, and etiology of ischemia all continued to have an increased risk of mortality; additionally, the post-operative course had a significant impact on long-term mortality with renal failure, hemorrhage, major adverse cardiac events, and respiratory failure all significantly associated with long-term mortality. Without adjusting for the post-operative course, patients who underwent OR had an increased risk of mortality, however, when controlling for the post-operative course, the survival benefit from ER was no longer significant. As noted previously, respiratory failure was more common in the OR cohort compared to the ER cohort (OR 19.9%, ER 8.3%, p=.003). Moreover, when all variables (i.e., comorbidities, clinical presentation, procedure, post-operative AEs) were included in the model expect for respiratory failure, procedure type was still significantly associated with mortality; when respiratory failure was then added into the model, the impact of procedure type was no longer significant, suggesting that the improved survival with ER is mediated through the decreased rate of post-operative respiratory failure events.

The secondary outcome of interest was long-term amputation. After excluding Rutherford III patients, there were 399 limbs available for analysis to delineate predictors of major amputation. The amputation rate for the entire cohort at 30 days, 1 year, and 5 years was 9.3±1.5%, 17.7±2.1% and 27.9±3.1%, respectively. Univariable analysis, using Kaplan Meier time-to-event analysis, determined significant predictors were male gender, coronary artery disease, history of prior coronary bypass, pre-operative renal failure, etiology of ischemia (Figure 2A), degree of ischemia at presentation (Figure 2B), previous ipsilateral vascular intervention, emergent bypass (Figure 2C), technical failure of procedure (Figure 2D), and respiratory failure.

Two multivariable models were created to determine predictors of amputation after ALI intervention. The first model (Table VI) controlled for pre-operative variables alone and demonstrated an increased risk of amputation at 5 years with advanced ischemia and thrombosed bypass etiology. The second model was created to include the addition of post-operative complications to the multivariable model (Table VII) to determine the impact of the postoperative course on long-term limb salvage. In this model, once controlling for clinical presentation, procedure type, and major post-operative AEs, degree of ischemia and the etiology of a thrombosed bypass continued to be strong predictors of amputation (HR: 2.57 and 3.53, respectively). Technical failure of a procedure was the strongest predictor of amputation (HR: 6.01). Once controlling for technical failure in the model, patients who underwent an OR had an almost 2-fold increased risk of amputation compared to ER (HR: 1.95, p=.022). Technical failure rates were significantly higher in ER compared to OR (22% vs. 11%, p=.046). Therefore, this analysis suggests that although revascularization failure rates are higher in ER, once these rates are held constant between ER and OR in a multivariable model, there is a significantly increased risk of amputation with OR compared to ER.

DISCUSSION

Contemporary acute limb ischemia patients are a unique cohort of vascular patients with an elevated acuity of illness given their high rates of comorbid conditions, decreased rates of

medical optimization and frequent association with malignancy.[2,4,5,10] Both older and more recent studies have demonstrated very poor outcomes of ALI patients, with 1-year mortality and amputation rates ranging from 16-42% and 11-37%, respectively.[2-5] Outcomes beyond one year have not been described recently, and furthermore, predictive risk factors for long-term outcomes in the modern era are unknown.

We hypothesized that predictors of long-term mortality and amputation would include a combination of clinical presentation characteristics, revascularization procedure type, and postoperative complications. Prior studies suggest that major post-operative AEs portend a negative impact on later outcomes beyond the initial hospitalization.[6] ALI patients are at risk of a tumultuous post-operative course secondary to their poor medical optimization and the need for urgent revascularization, which is associated with longer and more complicated procedures with higher blood loss.[4-6,11,20] Certain subsets of ALI patients will likely have a greater benefit from one type of revascularization technique over another given the heterogeneity of ALI patients with variable etiologies, comorbidities, and physiologic reserve.[21]

As demonstrated by our data, patients who underwent OR via open thrombectomy were significantly older, with higher rates of atrial fibrillation. These patients had a higher incidence of thromboembolic etiology with less underlying chronic arterial insufficiency and fewer previous lower extremity interventions. Therefore, these patients had anatomy favorable for successful thrombectomy to restore lower extremity arterial perfusion, and as a result, had the greatest rate of technical success (88%) with a low rate of amputation at 5-years (18%). However, given their association with advanced cardiac disease[22] and older age, these patients had a high rate of 5-year mortality (65%). Similar findings have been reported in the literature also documenting that these ALI patients have poor long-term mortality (60-70%) however with favorable amputation rates of 18-20%.[7,8,11,22,23]

Patients who required an emergent bypass typically had underlying chronic peripheral arterial disease with high rates of previous interventions and more advanced ischemia not amenable to ER given the prolonged time required for lysis or the underlying advanced atherosclerotic disease. This group had high rates of comorbidities (53% with CAD, 30% with atrial fibrillation, and 39% with COPD) placing them at risk for post-operative AEs, particularly with the physiologic stress of a prolonged, emergent arterial bypass. As a result, they had the highest rates of wound infections (21%), major cardiac events (15%) and respiratory failure (25%). This subpopulation represents the most challenging of the ALI patients to treat given their advance disease and comorbidities placing them at the highest risk not only for postoperative complications, but limb loss and mortality beyond the initial perioperative period, with a 27% amputation rate and a 65% mortality rate at 5 years.[4-6,24]

In comparison, the use of endovascular therapies was typically limited to a healthier subset of ALI patients. In our population, patients who underwent ER were younger, with less comorbidities such as atrial fibrillation and COPD and improved medical optimization with higher prevalence of clopidogrel and statin therapy. Moreover, these patients had a large proportion of thrombosed stents and a decreased degree of ischemia, limited to mostly Rutherford Class I (10%) and IIa (69%), allowing them to tolerate prolonged period of

ischemia to allow for complete revascularization with catheter directed thrombolytic therapy. In the postoperative period, ER patients had significantly less respiratory failure (8% vs. 20%), with similar rates of major cardiac events and hemorrhagic events. The low rates of hemorrhagic complications of ER (5-7%) likely represents the increasing experience with ER and the lack of concomitant therapeutic anticoagulation with intravenous heparin during lytic infusion.[5,12,13,20,25] While ER patients had a favorable AE profile, technical failure remains a significant disadvantage of this therapy, with previous reported rates of 20-50%, and 22% failure in our cohort.[6,11,12,14,15,20]

Given the differences between the patients undergoing OR and ER in a real world setting, multivariable models were utilized to delineate characteristics associated with poor long-term outcomes. The overall 5-year mortality rate was 54%, with the multivariable models identifying a number of prognostic factors, including increasing age, female gender, malignancy, fasciotomies, an etiology of embolic or in-situ thrombosis, renal failure, post-operative hemorrhage, major cardiac events and respiratory failure. Previous reports investigating risk factors for short-term mortality support these findings, with higher mortality in patients of advanced age,[11,17,26] malignancy,[2,10,26,27] in-situ thrombosis,[12,17] thromboembolic etiology, [11,17] renal failure,[20] and cardiac events.[3,20] When controlling for pre-operative variables alone, we found that OR had a 1.5-fold increased risk of long-term mortality compared to ER, however once controlling for the post-operative AE profile, in particular respiratory failure, there was no longer a difference between procedure types. In a previous study by Ouriel et al., improved mortality rates with ER were attributed to the decreased rates of cardiopulmonary complications with endovascular therapy.[3] Our analysis demonstrates how the post-operative course has a significant physiologic impact on this frail patient population and carries an impact over a long period of time beyond the initial hospitalization. Moreover, this indicates that the improved mortality rate seen in the ER cohort is likely a combination of healthier patients at baseline and the superior adverse event profile of ER, specifically, the decreased incidence of respiratory failure.

Similar analyses for delineating long-term amputation risk factors demonstrated that the strongest predictors were advanced ischemia, a thrombosed bypass, and technical failure of the procedure, which conferred a 6-fold increased risk of limb loss. Increasing severity of ischemia[17,20,27,28] and a thrombosed bypass[12,15] have also been identified as predictors of limb loss in previous studies. Amputation rates of patients undergoing thrombectomy and ER were similar in our cohort (18% and 17%, respectively) compared to 27% for emergent bypass likely given the less chronic nature of the arterial disease and higher embolic etiology of thrombectomy patients and the less advanced ischemia of the ER patients. When controlling for these differences in a multivariable model, there was no longer a significant increased risk of amputation with OR. However, once technical failure of the procedure is placed into the multivariable model, thereby holding technical failure rates the same for OR and ER, there was a 2-fold increased risk of amputation with OR. Therefore, this demonstrates that while revascularization failure rates are higher in ER, there is a significantly increased risk of amputation with successful OR compared to successful ER. Improved limb salvage with ER has been attributed to decreased endothelial damaged with catheter directed lysis[15,26] and the poor prognosis of an emergent bypass given the potential lack of adequate autologous conduit and need for a more distal target.[29] Regardless of

revascularization type, technical failure of the revascularization remains the strongest predictor of limb loss.

There were limitations of this study that should be acknowledged. Retrospective reviews carry an inherent risk of incomplete data collection as data is extrapolated from patient charts, however multiple sources of data were used in attempts to provide a complete and accurate database of ALI patients, such as operative reports, inpatient records, outpatient records and a the Social Security Death Index. Also inherent in a retrospective review is selection bias, and in this case it is the selection of the type of therapy chosen. However, given the large size of our cohort we adjusted for the patient differences between therapy types in a multivariable model, and in conjunction with our 5-year follow-up, we believe that we were are able to determine clinically meaningful risk factors for long-term outcomes.

CONCLUSION

ALI patients are a heterogeneous population with various ischemic etiologies, significant baseline comorbidities, and a low physiologic reserve. Some ALI patients will clearly, based on etiology and anatomy, obtain a more definitive revascularization with an acceptable adverse event profile with one revascularization type compared to another. However, some ALI patients are suited for either an OR or ER. Our study demonstrates that these patients require a careful evaluation of each individual's potential to develop a post-operative adverse event (particularly respiratory failure), as a complicated postoperative course drives the increased mortality of OR patients. In comparison, estimating the probability of technical success is also critical as technical failure is more likely with ER, however, when successful, ER has a significantly reduced risk of limb loss.

ACKNOLWEDGEMENTS

This research was supported, in part, by a NIH T32 Post-Doctoral Vascular Surgery Research Grant (*5T32HL098036-05*) awarded to Elizabeth Genovese MD, MS.

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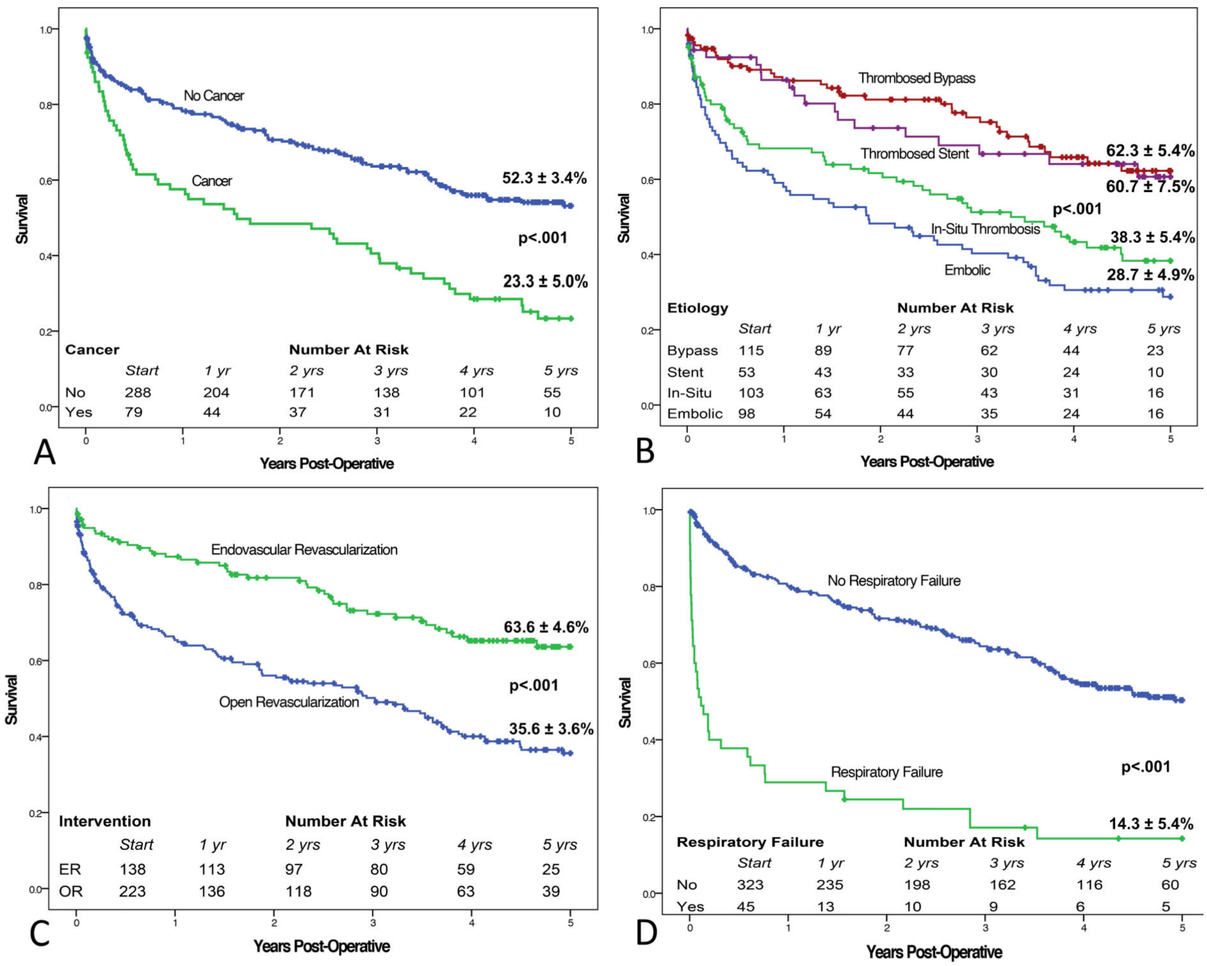

Figure 1.

Long-Term Kaplan-Meier Survival Curves Stratified by A) Cancer B) Etiology of Ischemia C) Type of Revascularization D) Post-Operative Respiratory Failure

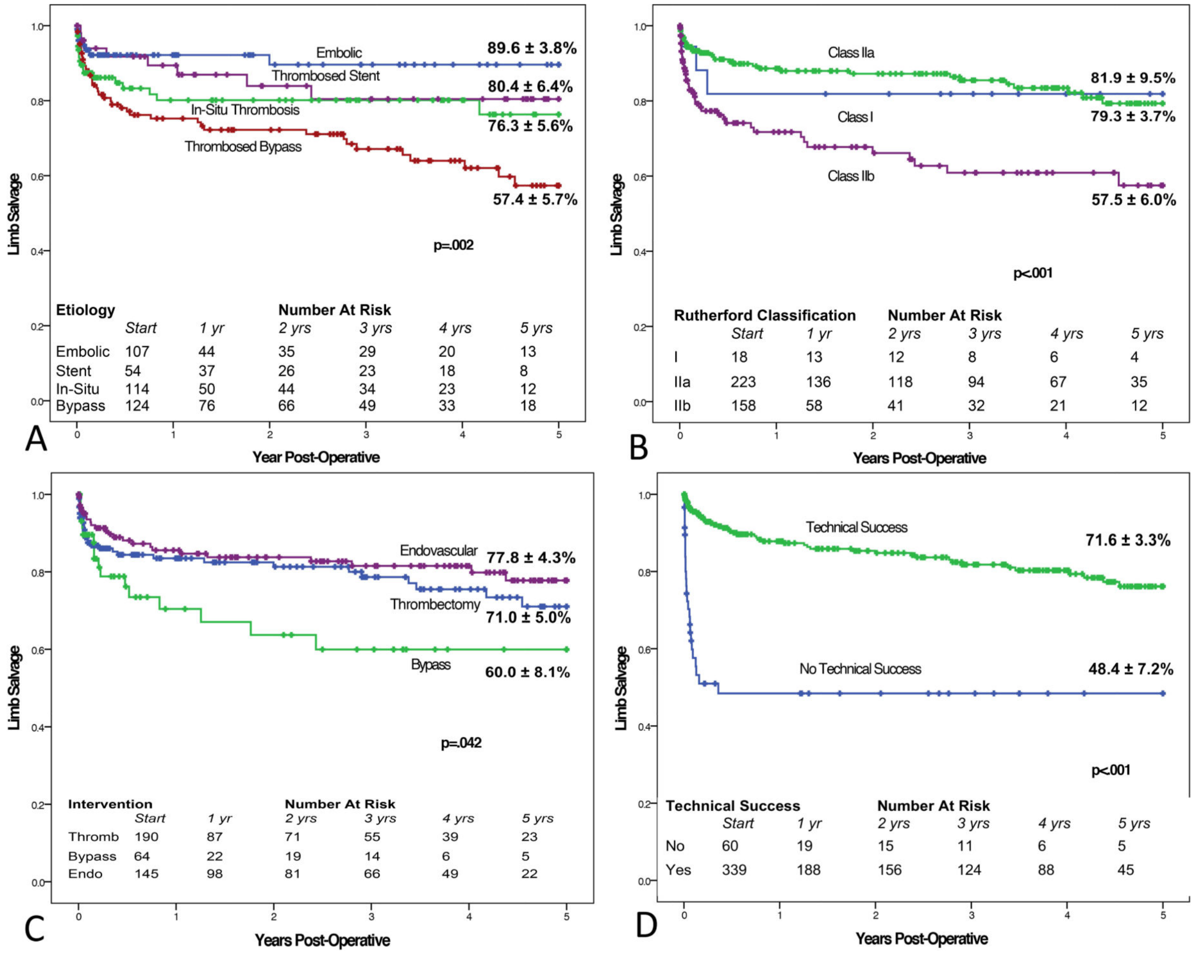

Figure 2.

Long-Term Kaplan-Meier Limb Salvage Curves Stratified by A) Etiology of Ischemia B) Rutherford Classification of Ischemia C) Type of Revascularization D) Technical Success

Table I

Incidence of Baseline Patient Characteristics for the Entire Cohort and by Intervention Type

Baseline Characteristic	Entire Cohort (n=411) *No. (%)*	Open Revascularization		Endovascular Revascularization (n=138) *No. (%)*	P-value *
		Thrombectomy (n=198) *No. (%)*	Bypass (n=75) No. (%)		
Demographics/ Comorbidities					
Gender, male	221 (53.8)	96 (48.5)	46 (61.3)	79 (57.2)	.099
Race, Caucasian	356 (90.6)	170 (90.4)	64 (90.1)	122 (91)	.972
Age, years, mean ± SD (range)	68.3±14.9 (18-96)	**71.1 ± 14.5 (32-95)**	**66.4± 13 (35-96)**	**65.2 ± 15.5 (18-96)**	**.001** †
Coronary Artery Disease	211 (51.6)	95 (48)	40 (53.3)	76 (55.9)	.345
Congestive Heart Failure	83 (20.3)	40 (20.2)	16 (21.3)	27 (19.9)	.967
Atrial Fibrillation	139 (33.9)	**87 (43.9)**	**22 (29.3)**	**30 (21.9)**	**<.001**
COPD	112 (27.4)	**51 (25.8)**	**29 (38.7)**	**32 (23.5)**	**.048**
Smoking, ever	236 (57.7)	**91 (46.0)**	**43 (58.1)**	**102 (74.5)**	**<.001**
Hypertension	321 (78.5)	155 (78.3)	61 (81.3)	105 (77.2)	.78
Hyperlipidemia	185 (45.2)	84 (42.4)	40 (53.3)	61 (44.9)	.269
Diabetes	139 (34)	63 (31.8)	23 (30.7)	53 (39)	.318
Stroke	64 (15.6)	33 (16.7)	14 (18.7)	17 (12.5)	.429
Cancer	92 (22.5)	46 (23.2)	17 (22.7)	29 (21.3)	.918
Renal Failure	17 (4.1)	6 (3)	5 (6.7)	6 (5.7)	.399
Pre-Operative Medications					
Coumadin	91 (22.5)	**54 (27.3)**	**16 (22.5)**	**21 (15.6)**	**.043**
Clopidogrel	84 (20.8)	**25 (12.6)**	**14 (19.7)**	**45 (33.3)**	**<.001**
Aspirin	157 (38.9)	66 (33.3)	29 (40.8)	62 (45.9)	.064
Statin	138 (34.4)	**56 (28.4)**	**21 (30)**	**61 (45.5)**	**.004**

SD= standard deviation, COPD=chronic obstructive pulmonary disease

* Chi-Squared or Fishers Exact test comparing incidence of pre-operative variables between intervention type

† Analysis of Variation test

Table II

Incidence of Clinical Presentation Variables for the Entire Cohort and by Intervention Type

Baseline Characteristic	Entire Cohort *No. (%)*	Open Revascularization		Endovascular Revascularization *No. (%)*	P-value*
		Thrombectomy *No. (%)*	Bypass *No. (%)*		
Previous Intervention	208 (46.7)	66 (30.4)	51 (61.4)	91 (62.8)	**<.001**
Rutherford Classification					
Class I	18 (4.4)	3 (1.1)		15 (10.3)	
Class IIa	223 (54.3)	123 (46.2)		100 (69.0)	
Class IIb	158 (38.4)	128 (48.1)		30 (20.7)	
Class III	12 (2.9)	12 (4.5)		0 (0)	**<.001**
Etiology of Acute Ischemia					
Embolic	119 (26.7)	92 (42.4)	6 (7.2)	21 (14.5)	
In-situ Thrombosis	127 (28.5)	67 (30.9)	30 (36.1)	30 (20.7)	
Thrombosed Bypass	142 (31.9)	51 (23.5)	38 (45.8)	53 (36.6)	
Thrombosed Stent	57 (12.8)	7 (3.2)	9 (10.8)	41 (28.3)	**<.001**

*Chi-Squared or Fishers Exact test comparing incidence of pre-operative variables between intervention type

Table III

Peri-Operative Adverse Events for the Entire Cohort and by Intervention Type

Adverse Event	Entire Cohort *No. (%)*	Open Revascularization		Endovascular Revascularization *No. (%)*	P-value*
		Thrombectomy *No. (%)*	Bypass *No. (%)*		
Technical Failure	71 (16)	**21(12.4)**	**12 (14.5)**	**32 (22.4)**	**.046**
Hematoma	34 (7.6)	20 (9.2)	4 (4.8)	10 (6.9)	.404
Wound Infection	32 (7.2)	**13 (6)**	**17 (20.5)**	**2 (1.4)**	**<.001**
Renal Failure	34 (7.6)	15 (6.9)	11 (13.3)	8 (5.5)	.091
Hemorrhagic Event	40 (9.1)	26 (12.1)	6 (7.7)	8 (5.5)	.093
Major Cardiac Event	47 (10.7)	22 (10.2)	12 (15.4)	13 (9)	.318
Respiratory Failure	71 (16.1)	**39 (18.1)**	**20 (24.7)**	**12 (8.3)**	**.003**

*Chi-Squared test comparing incidence of post-operative adverse events between intervention type

Table IV

Multivariable Model for Mortality at 5 years, Controlling for Clinical Presentation Only*

Variable †	*Hazard Ratio*	*95% CI*	*p-value*
Age, year	**1.04**	**1.02-1.05**	**<.001**
Gender, female	**1.46**	**1.04-2.07**	**.031**
Coronary Artery Disease	1.03	0.72-1.48	.862
Congestive Heart Failure	1.28	0.88-1.86	.195
Atrial Fibrillation	0.94	0.62-1.44	.784
COPD	**1.54**	**1.09-2.18**	**.015**
Smoking, ever	1.09	0.76-1.56	.656
Stroke	1.04	0.66-1.63	.874
Cancer	**1.81**	**1.28-2.54**	**.001**
Diabetes	1.30	0.94-1.81	.115
Renal Failure	**7.21**	**3.49-14.91**	**<.001**
Coumadin	1.22	0.82-1.80	.328
Aspirin	0.71	0.50-1.01	.056
Clopidogrel	0.88	0.54-1.44	.620
Rutherford Classification			
Class I *(ref)*			
Class IIa	**3.88**	**1.04-14.47**	**.044**
Class IIb	**4.80**	**1.30-17.87**	**.019**
Fasciotomy	**1.71**	**1.01-2.63**	**.016**
Etiology			
Embolic or In-Situ thrombosis ‡	**1.54**	**1.04-2.29**	**.032**
Open Revascularization §	**1.53**	**1.02-2.28**	**.038**

CI= Confidence Interval, COPD=chronic obstructive pulmonary disease

*Cox Proportional Hazards Model, 361 patients, Rutherford III patients excluded, overall model χ^2 value of 1691.4, p<.001

†All variables entered into the model had p<.15 on univariable Kaplan Meier analysis for predictors of 5-year mortality

‡Etiology; comparison of embolic or in-situ thrombosis compared to thrombosed bypass or stent

§Open revascularization risk compared to endovascular revascularization

Table V

Multivariable Model for 5-year Mortality, Controlling for Clinical Presentation and Post-Operative AEs[*]

Variable [†]	*Hazard Ratio*	*95% CI*	*p-value*
Age, year	**1.04**	**1.02-1.05**	**<.001**
Gender, female	**1.50**	**1.04-2.16**	**.031**
Coronary Artery Disease	1.02	0.70-1.49	.912
Congestive Heart Failure	1.19	0.81-1.74	.379
Atrial Fibrillation	0.79	0.51-1.22	.287
COPD	1.42	0.99-2.02	.051
Smoking, ever	0.93	0.65-1.34	.698
Stroke	0.84	0.52-1.35	.467
Cancer	**2.19**	**1.53-3.13**	**<.001**
Diabetes	1.11	0.80-1.56	.530
Coumadin	1.45	0.97-2.15	.067
Aspirin	0.79	0.55-1.45	.216
Clopidogrel	0.94	0.57-1.54	.800
Rutherford Classification			
Class I *(ref)*			
Class IIa	3.75	1.04-13.52	.043
Class IIb	3.99	1.10-14.40	.035
Fasciotomy	**1.69**	**1.07-2.67**	**.024**
Etiology [‡]			
Embolic or In-Situ thrombosis	**1.73**	**1.16-2.59**	**.007**
Open Revascularization[§]	1.44	0.94-2.2	.096
Technical Success	0.84	0.53-1.31	.434
Renal Failure	**4.70**	**2.48-8.91**	**<.001**
Hemorrhage	**2.25**	**1.33-3.82**	**.003**
Major Cardiac Event	**2.57**	**1.62-4.10**	**<.001**
Respiratory Failure	**2.72**	**1.68-4.40**	**<.001**

CI= Confidence Interval, COPD=chronic obstructive pulmonary disease

[*]Cox Proportional Hazards Model, 358 patients, Rutherford III patients excluded, overall model χ^2 value of 1600.4, p<.001

[†]All variables entered into the model had p<.15 on univariable Kaplan Meier analysis for predictors of 5-year mortality

[‡]Etiology; comparison of embolic or in-situ thrombosis compared to thrombosed bypass or stent

[§]Open revascularization risk compared to endovascular revascularization

Table VI

Multivariable Model for 5-year Amputation, Controlling for Clinical Presentation Only [*]

Variable [†]	*Hazard Ratio*	*95% CI*	*p-value*
Age, year	0.99	0.98-1.01	.468
Gender, female	0.65	0.39-1.09	.103
Coronary Artery Disease	1.36	0.82-2.27	.233
Diabetes	1.42	0.84-2.38	.191
Renal Failure	2.37	0.86-6.57	.096
Clopidogrel	1.30	0.76-2.20	.34
Rutherford Classification			
Class I	1.01	0.29-3.58	.984
Class IIa *(ref)* [‡]			
Class IIb	**2.92**	**1.78-4.81**	**<.001**
Etiology			
Embolic *(ref)*			
In-Situ Thrombosis	1.81	0.77-4.28	.177
Thrombosed Bypass	**3.53**	**1.59-7.86**	**.002**
Thrombosed Stent	1.62	0.58-4.58	.360
Open Revascularization	1.39	0.81-2.39	0.231

CI= Confidence Interval

[*] Cox Proportional Hazards Model, 385 limbs, Rutherford III patients excluded, overall model χ^2 value of 778.17, p<.001

[†] All variables entered into the model had p<.15 on univariable Kaplan Meier analysis for predictors of 5-year amputation

[‡] Rutherford Class IIa was used as a reference group as there was no significant difference in limb salvage rates between I and IIa in univariable analysis and there were a greater number of patients in the IIa category, allowing for a more stable model and comparison between Rutherford Classification IIa and IIb

Table VII

Multivariable Model for 5-year Amputation, Controlling for Clinical Presentation and Post-Operative AEs *

Variable †	***Hazard Ratio***	***95% CI***	***p-value***
Age, year	0.10	0.98-1.01	.626
Gender, female	0.69	0.41-1.16	.159
Coronary Artery Disease	1.39	0.82-2.36	.217
Diabetes	1.08	0.62-1.91	.783
Clopidogrel	1.49	0.87-2.57	.151
Rutherford Classification			
Class I	1.37	0.40-4.73	.622
Class IIa *(ref)* ‡			
Class IIb	**2.57**	**1.53-4.36**	**<.001**
Etiology			
Embolic *(ref)*			
In-Situ Thrombosis	1.77	0.74-4.25	.198
Thrombosed Bypass	**3.53**	**1.59-7.86**	**.002**
Thrombosed Stent	2.22	0.77-6.26	.132
Open Revascularization	**1.95**	**1.10-3.46**	**.022**
Technical Failure	**6.01**	**3.36-10.78**	**<.001**
Renal Failure	2.07	0.84-5.07	.113
Respiratory Failure	1.43	0.68-3.04	.350

CI= Confidence Interval

*Cox Proportional Hazards Model, 385 limbs, Rutherford III patients excluded, overall model χ^2 value of 736.715, p<.001

†All variables entered into the model had p<.15 on univariable Kaplan Meier analysis for predictors of 5-year amputation

‡Rutherford Class IIa was used as a reference group as there was no significant difference in limb salvage rates between I and IIa in univariable analysis and there were a greater number of patients in the IIa category, allowing for a more stable model and comparison between Rutherford Classification IIa and IIb