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# Predicting Early-, Intermediate-, and Long-Term Survival in Patients with Chronic Limb Threatening Ischemia Who Undergo Infrainguinal Revascularization

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## ABSTRACT

### Objectives:

Accurate survival prediction critically influences decision-making when caring for patients with chronic limb threatening ischemia (CLTI). The BASIL trial demonstrated that, in patients who survived >2 years, there was a significant advantage to infrainguinal bypass compared to endovascular intervention, which increased with time. Validated survival models for patients with CLTI are lacking.

### Methods:

The Vascular Quality Initiative was interrogated for patients who underwent infrainguinal bypass or endovascular intervention for CLTI (1/2003-2/2017). Cox survival models were generated using only pre-operative variables. Survival at 30 days, 2 years and 5 years was modeled separately. Patients were defined as low-risk (30-day survival >97% and 2-year survival >70%), medium-risk (30-day survival 95-97% or 2-year survival 50-70%), or high-risk (30-day survival <95% or 2-year survival <50%).

### Results:

Among 38,470 unique CLTI patients, 63% (n=24,214) underwent endovascular intervention and 37% (n=14,256) underwent infrainguinal bypass. Kaplan-Meier estimates of overall survival at 30 days, 2 years, and 5 years were 98%, 81%, and 69%, respectively. The proportion of patients in the low-, medium-, and high-risk groups was 84%, 10%, and 6.5%, respectively. Patients in the low-risk group were significantly less likely to undergo endovascular intervention compared to those in the high-risk group (low-risk, 59% endovascular; high-risk, 75% endovascular; p<.0001). Independent predictors of death were similar in all three models, with greatest magnitude of effect associated with age >80 years, oxygen-dependent chronic obstructive pulmonary disease, Stage 5 chronic kidney disease, and bedbound status. The c-index for the 30-day model, 2-year model, and 5-year model was 0.76, 0.72, and 0.71, respectively. Procedure type (open or endovascular) was not significant in any models, and did not impact c-indices.

### Conclusions:

These survival prediction models, derived from a large, US cohort of patients who underwent revascularization for CLTI, demonstrated good performance and should be validated. Most CLTI patients considered as candidates for limb salvage were of average perioperative risk, and were predicted to survive beyond 2 years. These models can discriminate patients into low-, medium-, and high-risk groups to facilitate evidence-based revascularization recommendations that are consistent with current treatment guidelines.

## INTRODUCTION

Patients with chronic limb threatening ischemia (CLTI) have markedly reduced life expectancy when compared to age-matched controls.(1) Yet, survival estimates have varied in the literature (Table 1), making evidence-based predictions of survival challenging. While decision-making in the management of CLTI is complex and multifaceted, the most basic step in the decision tree is determining the likelihood that the patient can survive the procedure, and has reasonable life expectancy ahead of him/her. Given the heterogeneity of the disease process and the limited high quality evidence currently available, the Society for Vascular Surgery (SVS) Lower Extremity Guidelines Writing Group was established to examine available evidence, identify high-priority research questions,(2, 3) develop improved classification schemes,(4) objective performance measures for evaluating treatment methods,(5) and define best practices [not yet published]. In 2014, the SVS announced its participation in a global collaborative intended to develop international clinical practice guidelines in the management of peripheral artery disease; this collaboration seeks high-quality evidence on which to base its recommendations.(6)

While three large trials are planned or underway throughout the world,(7-9) to date, the only randomized controlled trial comparing open lower extremity bypass (LEB) to endovascular intervention for the management of limb ischemia remains the Bypass versus Angioplasty in Severe Limb Ischemia (BASIL) trial, published in 2005.(10) Intention-to-treat analyses of these data demonstrated that, among those patients who survived two years, there was a significant improvement in overall and amputation-free survival among those randomized to LEB. This finding has led many clinicians to favor the use of LEB for those patients they believe have a good likelihood of 2-year survival and available autogenous vein conduit. This approach has

been endorsed in prior multi-specialty practice guidelines.(11) In addition to long-term survival, peri-operative risk plays a major role in determining suitability for limb salvage attempts and selection of revascularization approach, and may be a dominant consideration in frail patients or those with advanced comorbidities.

It is disappointing to note that evidence to guide survival prognostication in this patient population is lacking. While the BASIL authors published a survival prediction model for this purpose in 2010,(12) its external validity is unclear, and many of the variables are not readily available. Other models for prediction of amputation-free survival have been developed from registries and clinical trials,(13-17) but their generalizability to a contemporary, 'real world' US population of CLTI patients is not known. We sought to create a prediction model for 30-day, 2-year, and 5-year survival using a Vascular Quality Initiative cohort treated with infrainguinal revascularization (endovascular intervention or open bypass) for CLTI. This model can be applied to discriminate between those with low-, medium-, and high-risk for peri-operative (30-day) and 2-year mortality, which may aid in clinical decision-making.

## METHODS

**Study Cohort:** Prospectively collected data from the VQI database were retrospectively reviewed to identify all patients who underwent peripheral vascular intervention (PVI) or infrainguinal lower extremity bypass (LEB) between January 1, 2003 and February 1, 2017. The VQI is a national cooperative quality improvement initiative developed to prospectively collect data and outcomes for patients undergoing vascular surgical procedures. It is comprised of over 3000 physicians from >400 academic and community medical centers across the United States. Details of this registry are available online (www.vascularqualityinitiative.org). Data are physician-reported at the time of operation for all consecutive cases, and include preoperative, intraoperative, and in-hospital postoperative details. Follow up data are entered at approximately one year postoperatively. Date of death is cross-referenced with the Social Security Death Index and Medicare Claims. All information is sent to a central data repository where it is aggregated and audited. Research analysts are blinded to patient, surgeon, and hospital identity.

Two registries from the VQI (peripheral vascular intervention and infrainguinal lower extremity bypass) were queried for all consecutive patients between 2003 and 2014 for CLTI. CLTI was defined as rest pain and/or tissue loss. For patients in whom multiple revascularization procedures were performed, the first revascularization procedure was the only one included in order to ensure that all analyses were performed on unique patients. Peripheral vascular intervention included endovascular interventions on the femoropopliteal and tibial segments; hybrid procedures with open femoral exposure and endarterectomy were also included. Patients who underwent peripheral vascular intervention performed on the aortoiliac segment, with or without concomitant infrainguinal intervention, were excluded. All interventional modalities were included (angioplasty alone, with any type of balloon, or in combination with any stenting

or atherectomy). Lower extremity bypass included open infrainguinal revascularization procedures: femoral-popliteal bypass, femoral-tibial bypass, and distal origin bypass. There were no exclusions based on the type of provider performing the procedure. Patients who underwent concomitant bypass or endovascular intervention proximal to the infrainguinal bypass inflow were excluded in order to exclude patients with aortoiliac occlusive disease. Patients who underwent emergent procedures were excluded. Patients were also excluded if data pertaining to the primary endpoint, death, was missing.

Use of the VQI dataset was reviewed by the University of Massachusetts Medical School Institutional Review Board and deemed exempt, and patient consent was not required.

**Covariates Examined:** Patient information for >100 clinical and demographic variables (available at www.vascularqualityinitiative.org) was collected. Demographic information included age at the time of the procedure, sex, and race. Comorbidities examined included coronary artery disease (CAD; history of MI without current symptoms, stable angina, or unstable angina or MI within the past 6 months), chronic obstructive pulmonary disease (COPD; medication-dependent or home oxygen-dependent), congestive heart failure (CHF; by history), diabetes mellitus (DM; diet controlled and medication-dependent), hypertension (HTN; history of hypertension or blood pressure ≥140/90 mm Hg on the preoperative evaluation), and history of tobacco use (never, <1 year prior, or current). Renal disease was categorized by stages of chronic kidney disease (CKD; stages 1-5); this was assigned by calculating estimated glomerular filtration rate (eGFR) according to the CKD Epidemiology Collaboration equation (https://www.kidney.org/content/ckd-epi-creatinine-equation-2009). Height in meters (m) and

weight in kilograms (kg) was collected, and body mass index (BMI) calculated according to the formula: BMI = weight (kg) / [height (m)]$^2$. History of previous coronary revascularization included both coronary artery bypass graft and percutaneous coronary intervention. History of previous ipsilateral revascularization included any ipsilateral arterial bypass or previous peripheral vascular intervention. Previous major amputation included both above- and below-knee operations. Information on functional status included preoperative ambulation status (independent, with assistance, wheelchair-bound, or bedbound) and living situation (nursing home, or at home/homeless). Information on the presence of infection, and characteristics of ulceration were not available; tissue loss was categorized only as present or absent. While ankle-brachial index and toe-brachial index are collected, they were found to be missing (both limbs) in >40% (n=15714), and therefore these variables were not used in any of the models.

**Endpoints:** The primary endpoint was survival, defined as freedom from all-cause mortality. The primary endpoint was survival at two years; survival at 30 days and at five years were modeled as secondary endpoints. The unit of analysis was at the patient-level, first revascularization, regardless of whether the patient required repeat revascularization procedures on either extremity.

**Risk groups:** We pre-defined high-, medium-, and low-risk groups based on both peri-operative and long-term mortality. For each patient, the models were applied to calculate their associated probability of survival at both the 30-day time point, and the 2-year time point; this allowed them to then be assigned into risk groups accordingly. High-risk was defined as 30-day

survival <95% and/or 2-year survival <50%. Medium risk was defined as 30-day survival 95-97% and/or 2-year survival 50-70%. Low-risk was defined as 30-day survival >97% and 2-year survival >70%. The high-risk definition was chosen in accordance with recommendations from the Global Vascular Guidelines writing group (personal communication; publication under review). We also assessed the distribution according to the individual time-point risk definitions of 30-day risk and 2-year risk.

**Statistical Analyses:** Univariate analyses of explanatory variables were performed using Kaplan Meier methods, with patients censored at death or loss to follow-up, whichever came first. Given the statistical power associated with a cohort of this size, a more stringent threshold was chosen for univariate screening ($p<0.001$) for inclusion in the multivariable models. Cox proportional hazards models for the outcomes of 30-day, 2-year, and 5-year survival were constructed, using backwards stepwise elimination, with patients censored at death or loss to follow-up, whichever came first. Models were tested for violations of the proportionality assumption and for multicollinearity. Where variables did violate the proportionality assumption, Nagelkerke's R-squared was then calculated to determine the amount of variance explained in the model without, compared to with, those variables. We also created interaction terms with time for each of the variables in each of the models that did violate the proportionality assumption. These results are available in an online appendix. We tested all covariates in the final models for multicollinearity by examining tolerance and variance inflation. There were no indications of multicollinearity between the covariates.

Internal validation of the models included assessment of discrimination and calibration. Discrimination was assessed using the c-index. Harrell's c-index is a measure of the model's predictive accuracy, analogous to the c-statistic, or area under the receiver-operator characteristic curve, but appropriate for time-to-event analyses with censoring. Calibration was assessed using the Hosmer-May goodness of fit test. This test evaluates calibration by testing if a variable representing the risk groups themselves adds predictive ability. If this test is statistically significant, then the model does not perform equally well across risk groups, and is not well calibrated. While additional methods of internal validation are possible, these cannot replace the need for external validation, which was not conducted as part of this report. Analysis was conducted using SAS, v9.4 (Cary, NC).

## RESULTS

**Cohort characteristics.** Using the VQI database, 38,470 unique patients were identified who underwent infra-inguinal revascularization for CLTI (**Table 2**). Of these, 24,214 underwent PVI (63%), and 14,256 underwent LEB (37%). Revascularization was more commonly performed for tissue loss than for rest pain in both groups (tissue loss: PVI, n=18,104, 75%; LEB, n=8692, 61%). The cohort was predominantly white (n=29,061, 76%), male (n=23,533, 61%), and between the ages of 60 and 80 (n=22,135, 58%). While some traditional vascular risk factors were common (70% (n=27,033) were former or current smokers, and 63% (n=24,328) were diabetic), others were less so (31% (n=11,715) had any CAD). The majority (90%) of patients were ambulatory (independent or with assistance); the PVI cohort included more patients who were wheelchair- or bed-bound (11% in the PVI group, versus 6.8% in the LEB group). Notably, 50% of LEB performed were in patients with a prior history of ipsilateral limb revascularization (indication and nature of the pre-VQI procedure unknown).

The PVI database was added to VQI in 2008. There has been an increase in the proportion of PVI: 67% PVI in the 2013-17 time period compared with 57% PVI in the 2008-2012 time period.

**Survival.** Among the total cohort, the 30-day survival estimate was 98% (standard error (SE) = 0.0007), the 2-year survival estimate was 81% (SE=0.002), and the 5-year survival estimate was 69% (SE=0.004) (**Figure 1a**). Survival was significantly different between the LEB and PVI cohorts (log rank, $p<0.01$), with 5-year survival estimates of 71% (SE=0.005) in

the LEB group and 68% (SE=0.005) in the PVI group (**Figure 1b**). Deaths over the first 30 days postoperatively were distributed evenly, without a clear peak time-point.

**Predictors of survival.** On univariate analysis, nearly all covariates met criteria for inclusion in the adjusted survival prediction models; this was true for all three time-points (30-day, 2-year, and 5-year). After adjustment with backwards-stepwise selection, there were 9 covariates in the 30-day model, 12 covariates in the 2-year model, and 13 covariates in the 5-year model (**Table 3**). Of note, procedure type (open or endovascular) was not significant in any of the three models. There was considerable similarity between the models in terms of covariates, and magnitudes of effect (**Table 4**), with increasing age, worsening chronic kidney disease, and impaired ambulation status conferring the greatest hazard of death. Preoperative statin use and non-white race were associated with improved survival in all three models.

Upon testing of the 30-day mortality model, "indication" (rest pain or tissue loss) violated the proportional hazards assumption. This variable was left in the final model for face validity after calculating Nagelkerke's R square (which was 0.002) comparing the model with and without indication. This means 0.2% of the variance in the hazard can be explained by the full model relative to the model without the covariate that didn't meet the proportional hazards assumption. In the 2-year mortality model, CAD and pre-op ambulation violated the proportional hazards assumption. Full model results that include these interaction terms can be found in a supplemental online Table 1A-C.

In testing for multicollinearity, the tests for correlation between each of the variables were almost all statistically significant. However, the largest Pearson correlation coefficient was

0.36. Since this correlation is considered at the medium range for correlations, we elected to keep these covariates in our final model.

**Internal validation of models.** All three models demonstrated acceptable discrimination, with the following c-indices: 30-day, c=0.76, 2-year, c=0.72, and 5-year c= 0.71. Sensitivity and specificity of the 2-year survival model was 90.2% and 31%, respectively; therefore, the positive predictive value is approximately 85%, meaning that 85% of the time that a patient is predicted to survive 2 years, that prediction is accurate. The negative predictive value is 43%, meaning that 43% of the time that a patient is not predicted to survive 2 years, that prediction is accurate. All three models demonstrated inadequate calibration on Hosmer-May goodness of fit testing, all $p<0.05$. In order to better understand this, calibration tables according to deciles of risk were constructed. For the 30-day survival model ($p=0.024$), the calibration table demonstrated that those in the 9th decile of risk had more deaths observed than expected ($p=0.01$). The other deciles of risk fit well with this model. For 2-year survival model ($p< 0.0001$), the calibration table showed that the model only fit well for the 4th, 5th, and 7th deciles of risk. For 5-year survival model ($p<0.0001$), the calibration table showed that the model does not fit well for the lowest and highest deciles of risk. Given that Hosmer-May testing may be overly sensitive in a dataset of this size, calibration curves were generated, demonstrating where the models perform best and the amount of deviation, graphically (**Figure 2**).

**Risk groups.** Most patients were in the low-risk group (84%); 10% were in the medium-risk group, and 6.5% in the high-risk group (**Figure 3**). PVI was performed more commonly in

all three groups, but the proportion increased as risk increased (low-risk, PVI=59%; medium-risk, PVI=70%; high-risk, PVI=75%) (**Figure 3**). The baseline survival for the 30-day model is 0.997. The baseline survival for the 2-year model is 0.952. The equation for the Cox survival model is:

$h(t, X) = h_0(t) \exp(\sum \beta_i x_i)$ where $X = (x_1, x_2, \ldots, x_p)$ are the covariates, and $h_0(t)$ is the baseline hazard.

Beta coefficients are provided in Tables 3A and 3B; and samples calculations are provided in Table 5. Once the 30-day and 2-year probability of survival is calculated for each patient, we used 1 - probability of survival to get probability of mortality. When the 30-day probability of survival >0.97 and 2-year probability of survival >0.70 then patient is considered low risk. If (30-day probability of survival >0.97 and 2-year probability of survival >= 0.50 and 2-year probability <=0.7) or (30-day probability of survival <=0.97 but >0.95 and 2-year probability of survival >=0.5) the patient is considered at medium risk. And high risk patients are those with (2-year survival probability <0.5 and any non-missing 30-day probability of survival) or (30-day survival probability <0.95 and any non-missing 2-year probability of survival).

Of those patients who were "high risk" (n=2176) based on the "30-day survival <95%" criterion, 37% (n=815) also met criteria based on the "2-year survival <50%" criterion. Among those patients who were "low risk" (n=27,952) based on the "30-day survival >97%" criterion, 100% also met criteria based on the "2-year survival >70%" criterion. When separated out according to risk at the individual time-points (30-day survival risk, and 2-year survival risk

groups), the distribution patterns were similar to the distribution of the composite endpoint risk with >80% of patients in the low-risk group, and <10% in the high-risk group.

Kaplan Meier survival analysis, stratified by risk group demonstrated significant differences when truncated at 2 years (log-rank, $p<0.01$), and when truncated at 5 years (log-rank, $p<0.01$) (**Figure 4**). The 5-year survival estimates were: low-risk 77% (SE=0.004), medium-risk 50% (SE=0.014), and high-risk 43% (SE=0. 017).

Kaplan Meier survival analysis, stratified by risk group, but dichotomized into "high risk" and "low/medium risk" were significantly different on log-rank analysis ($p<0.01$) (**Figure 5).**

## DISCUSSION

The decision to revascularize a patient with CLTI requires careful consideration of multiple factors including the severity of limb threat, the anatomic pattern of disease, conduit availability, functional status, perioperative risk, and overall life expectancy. An evidence-based approach that incorporates both perioperative and longer-term survival estimation is required for shared-decision making. Using readily obtained preoperative variables, patients with CLTI can be stratified into three risk groups to determine their likelihood of survival following revascularization. The models described, derived from a contemporary US cohort of patients, demonstrated good discrimination and should be validated externally.

Among nearly 40,000 patients who underwent infra-inguinal revascularization for CLTI, the 30-day survival estimate was 98%, the 2-year survival estimate was 81%, and the 5-year survival estimate was 69%. Survival information was available for 100% of the cohort. While the 30-day estimates are in line with previous published reports (30-day mortality rate of 3.1% in the Finnvasc registry),(13) the 2- and 5-year estimates were more favorable than some prior studies (**Table 1**). The explanation for this remains unclear. While there has been some evidence of a trend towards improved survival over time, this has been inconsistent (in 2005, the BASIL investigators reported a 2-year survival of approximately 70%,(10) and in 2015, a Japanese cohort reported a 2-year survival of 64%(17)). One possible explanation for the favorable survival seen in our study may relate to the overall high compliance with long-term statin therapy (66% were on a statin preoperatively). While still arguably below the goal for statin utilization in this population, this is approximately double the use reported in the BASIL trial, and 20% higher than in the PREVENT III study.

Despite these favorable results in our cohort of CLTI patients, with most patients classified as low-risk (84%), nearly 2/3 of the total cohort were treated using an endovascular approach. These data mirror reports from other large registry studies, likely reflecting considerations beyond survival estimation alone.(18, 19) Within each risk group, endovascular intervention was used more commonly. However, the proportion of endovascular treatment rose as risk group increased, with endovascular intervention used in 75% of high-risk patients, compared with 59% in the low-risk group. Notably, the low-risk subgroup (comprising 84% of all patients undergoing infra-inguinal revascularization for CLTI in the VQI database) enjoyed a >75% survival out to five years. Given the significant recrudescence of foot ulcerations and CLTI symptoms, durability of revascularization is likely to be an important consideration for many such patients.

Of note, while the majority was treated with an endovascular approach, 37% of the cohort underwent open revascularization as their first intervention for CLTI. This challenges a commonly reported trend toward an endovascular-first approach,(20) with estimates suggesting this occurs as much as 80% of the time.(18, 21) Most authors describing trends in limb revascularization focus on procedure volumes rather than unique patients, thus the discrepancy likely reflects the higher incidence of repeat procedures associated with endovascular interventions.

Similar to other reports of risk factors for mortality in this population,(12, 22-25) increasing age, worsening CKD, and worsening functional status were important predictors of

worse outcomes. Our model differed from these previous reports in terms of the cohort studied; that is, our study was confined to CLTI patients who underwent vascular interventions, and included both open and endovascular revascularization strategies. The factors we identified were predictive across all three models. In addition, while the risk groups were defined using a composite criterion (a combination of 30-day hazard and 2-year hazard), there was significant overlap – that is, those patients who were high-risk for impaired 30-day survival were typically the same group that were high risk for impaired 2-year survival. And conversely, those with low risk for impaired 30-day survival were the same group that was low risk for impaired 2-year survival. These results, taken together, suggest that identification of these patients can be done with confidence. The increased use of endovascular therapy as risk increased may imply that surgeons are, in fact, identifying these two extreme ends of the spectrum, and making treatment recommendations accordingly. However, if current societal treatment guidelines were adhered to,(11, 26) the proportion of patients treated with endovascular and open revascularization would change significantly. Far more low-risk patients, as defined by survival predictions, are undergoing endovascular treatment than evidence-based recommendations would predict. In fact, the majority of patients in the total cohort would be considered standard survival risk for open revascularization. There are several factors that may contribute to this, including the anatomic pattern of disease, the severity of limb threat, and patient/surgeon preference; survival prediction alone should not dictate treatment choice. This may reflect an increasing preference for initial endovascular intervention; however, there is evidence this may not be a benign strategy in CLTI. A history of endovascular intervention prior to open bypass has been associated with worse outcomes, challenging the concept that an endo-first strategy does not "burn any bridges."(10, 27, 28) In agreement with Jones et al,(29) these data demonstrate that

LEB is commonly being performed after one or more prior revascularization failures in the same limb (50% in the current VQI cohort). Higher quality evidence comparing the effectiveness of endovascular and open revascularization across the full clinical and anatomic spectrum is sorely needed to guide treatment choices. Our data suggest that patient survival beyond 2 and even 5 years should be strongly considered within the competing risk calculations for many, if not most, CLTI patients who are currently treated with revascularization.

Other prediction models have been published to facilitate decision making in CLTI.(4, 13, 16, 17, 30-32) Many of these have used a composite endpoint of amputation-free survival (AFS). AFS is an attractive endpoint for the treating provider, because it addresses both survival, without which there cannot be treatment "success," but also addresses limb salvage, which is the surgeon's goal of revascularization. However, these models have not performed particularly well on external validations, perhaps due to the discrepancy between predictors of survival and predictors of limb salvage. They have not gained widespread use in clinical practice, perhaps because their direct impact on decision-making is unclear. Instead, they may be better suited to benchmarking outcomes of revascularization.(16) The BASIL model was the only one that was derived from a cohort of CLTI patients who underwent both endovascular and open revascularization, but this was a highly selected group that met equipoise considerations by these investigators and may not reflect contemporary practice. The model described herein offers the advantage of being derived from a large, heterogeneous cohort, which may better represent real world practice in the US. It is also focused on survival only, for which we may have increased predictive ability, compared with the composite endpoint, AFS. The value of decisions tools such as this rests in providing objective criteria, and relative weighting, to support clinical judgment and increase evidence-based care of the vascular patient.

Limitations of this analysis include a selection bias related to the procedure-based nature of VQI. That is, only patients who were deemed operative candidates were included, while those with presumably the most limited survival may have been treated with primary amputation or palliation. However, a recent systematic analysis of CLTI patients who did not undergo revascularization reported a 1-year mortality rate of 22%.(33) A prospective study based on all-comers referred for attempted limb salvage is needed. In addition, the diagnosis of CLTI is based on the physician's report of clinical symptoms; an objective measure of perfusion was not used. Although ankle-brachial index and toe-brachial index are recognized for their predictive value for survival, they were not included.(34, 35) These are available data fields in VQI that could also be utilized for hemodynamic corroboration of the CLTI diagnosis; however these data are missing in >40% of records. It is important to note that the models did not perform well on tests of calibration; the reasons for this are not clear, but may relate to the over-sensitivity of Hosmer-May testing in a dataset of this size. While measures of internal discrimination were favorable, an external validation has not yet been performed. Without an external validation, and given the possibility of selection bias, these models may be more suited to risk stratification rather than preoperative prediction. However, with a cohort of this size, from real-world practice, we would argue that it may approximate the US patient population, making external validation, at least within the US, statistically important but potentially less critical from a clinical perspective. It would be of great interest to validate these models in other national and international registries to reflect global demographics, care delivery and practice patterns in CLTI populations. It would also be interesting to compare predictive ability of models such as this, with those that could theoretically be obtained with machine learning, as described for other clinical predictions.(36)

Despite these constraints, the prediction models herein offer an important opportunity to better align clinical practice with evidence-based societal treatment guidelines. The majority of patients undergoing invasive vascular treatment for CLTI may be considered appropriate for open revascularization, from a survival perspective, hence other factors such as the anatomic pattern of disease and severity of limb threat should be dominant considerations in selecting the optimal revascularization strategy. These models may be transformed into an easy-to-use mobile app allowing for bedside assessment of peri-operative and long-term survival in CLTI patients (**Figure 6**). Several examples of the resultant output are presented (**Table 5**). As with all prediction models, these should be used as a tool to assist in decision making, not as an automated algorithm for care. In addition, attention should be paid to modifiable components of risk including appropriate use of cardioprotective medications such as antiplatelet agents and statins, as well as smoking cessation, in accordance with practice guidelines.

## CONCLUSION

Among a contemporary US cohort of 38,470 patients who underwent infra-inguinal revascularization for CLTI, the 30-day survival estimate was 98%, the 2-year survival estimate was 81%, and the 5-year survival estimate was 69%. Patients could be clearly delineated into one of three risk groups for impaired survival, using preoperatively available covariates. In accordance with international societal guidelines, and other critical factors (severity of limb threat, anatomic pattern of disease, conduit availability) these survival prediction models may help to guide treatment recommendations and shared decision-making with patients and their families.

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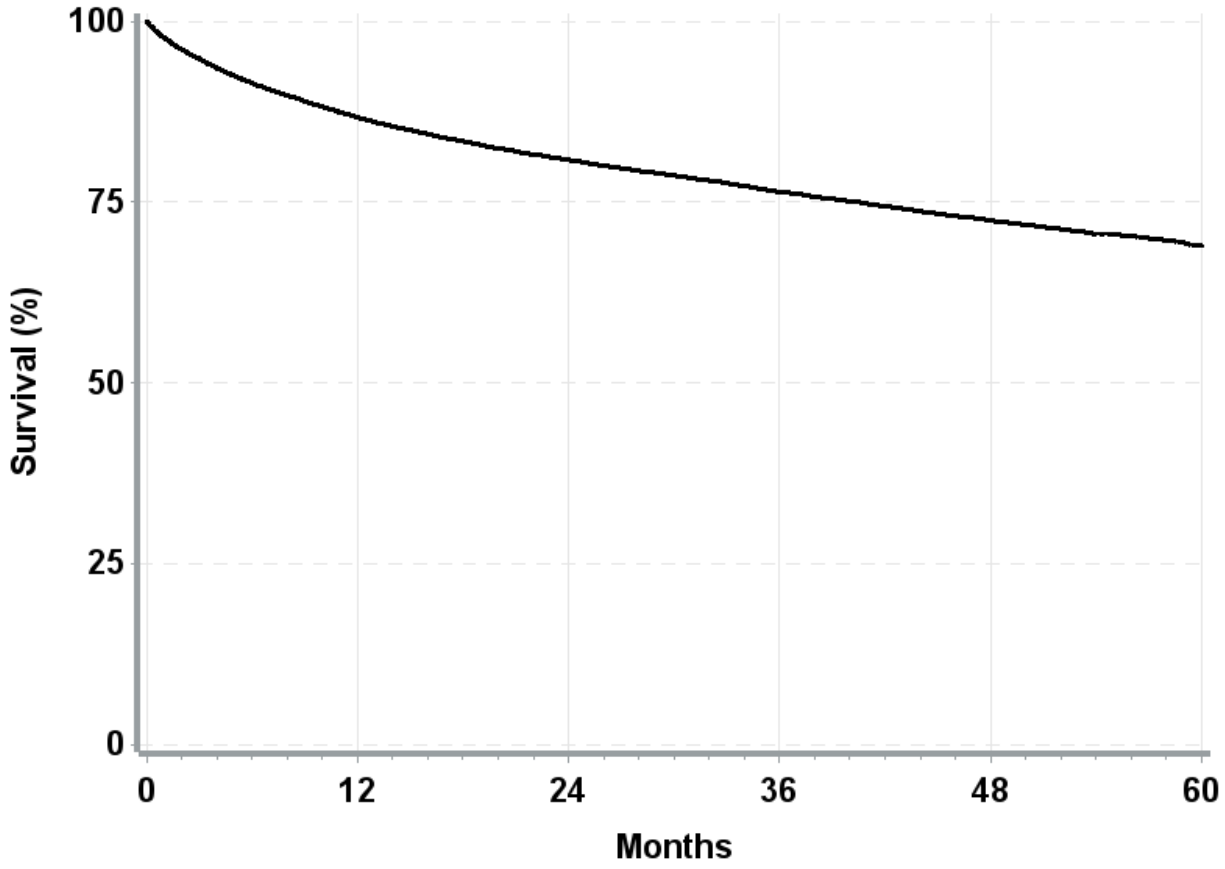
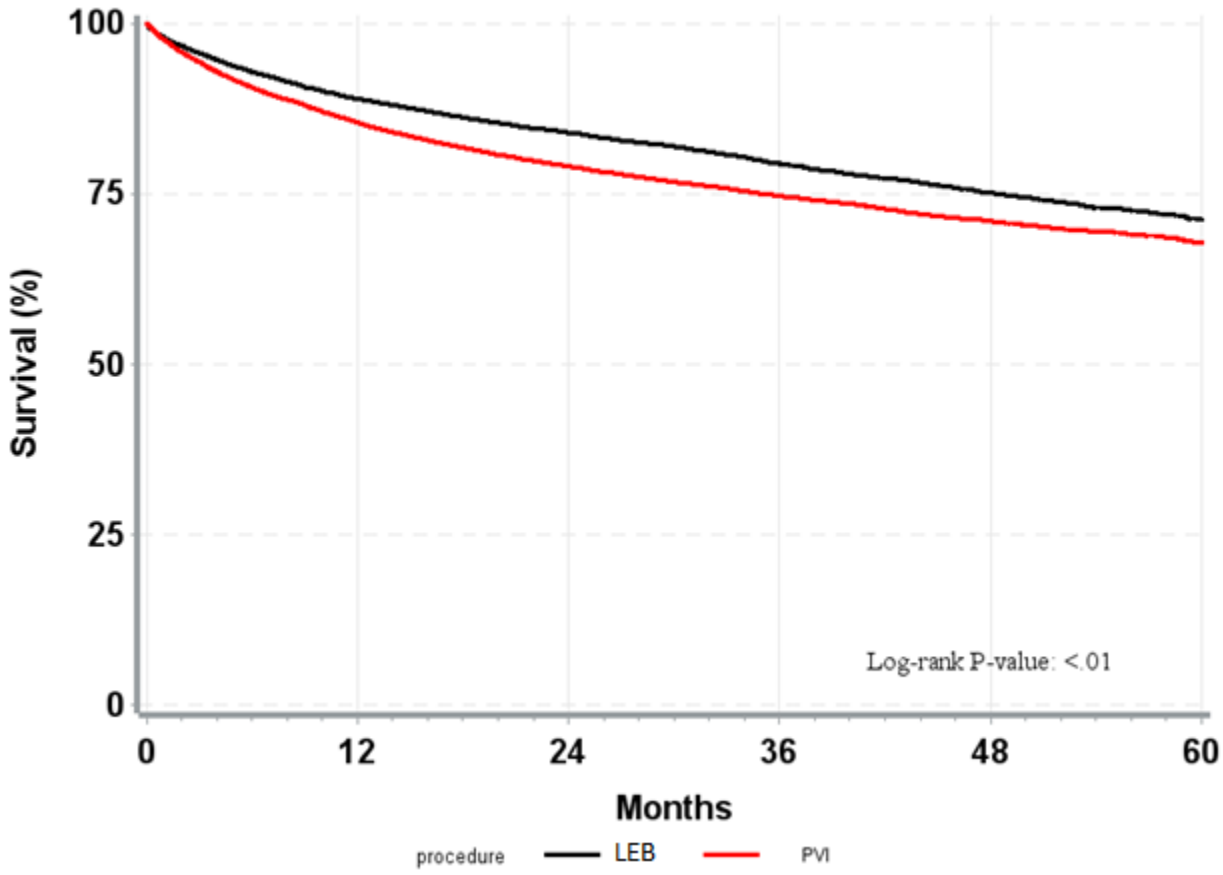
**Figure 1. Kaplan Meier analysis of survival in the (A) total cohort (n=38,470 with 8176 deaths over 5 years), and (B) stratified by procedure type (lower extremity bypass, n=14,256 with 2748 deaths over 5 years; peripheral vascular intervention, n=24,214 with 5428 deaths over 5 years).**

A.




| Months: | 1 | 24 | 60 |
|---|---|---|---|
| Number at risk: | 37551 | 19035 | 3503 |
| Survival estimate: | 98% | 81% | 69% |
| Survival SE: | 0.0007 | 0.002 | 0.004 |

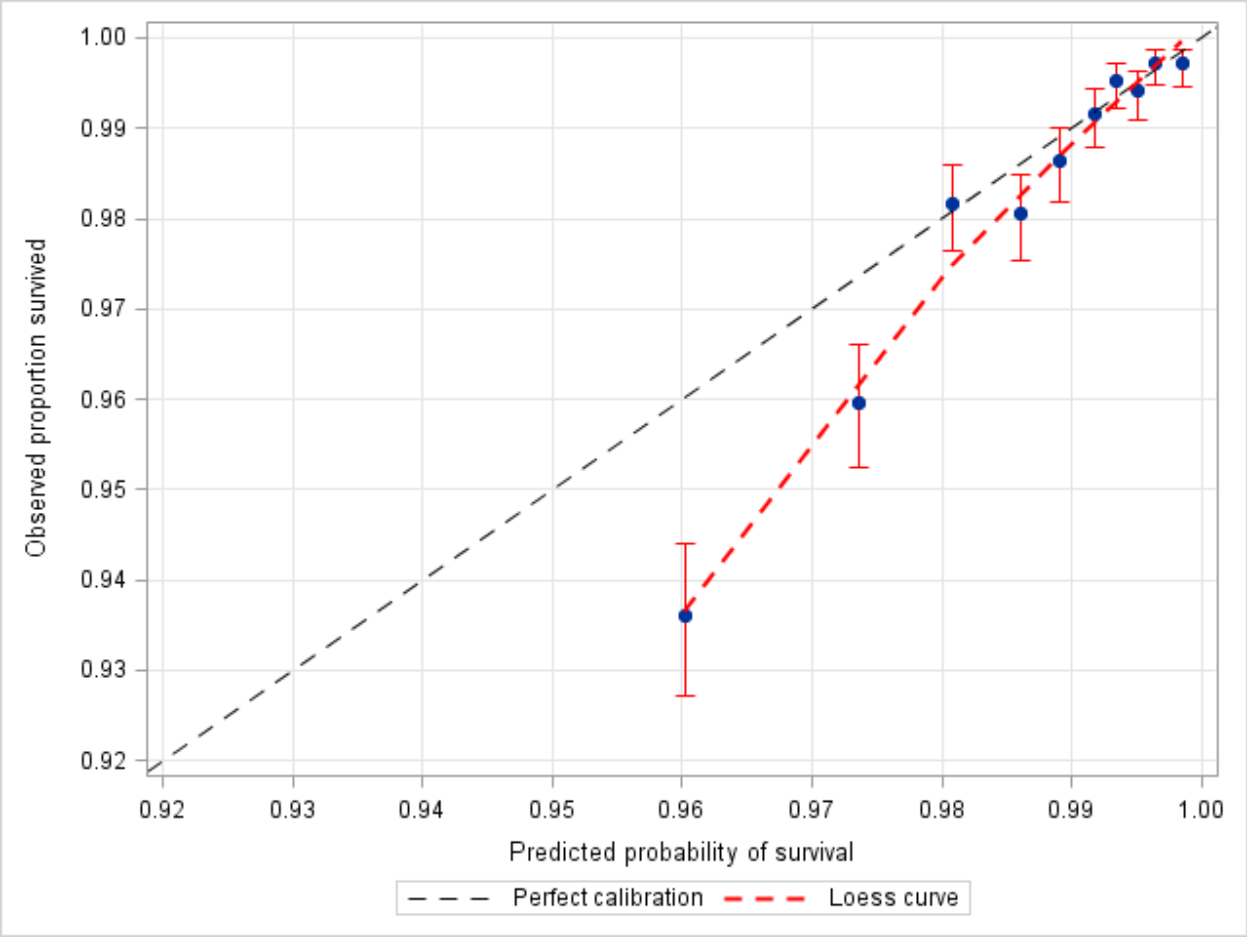
B.




| Months | 1 | 24 | 60 |
|---|---|---|---|
| LEB | | | |
| Number at risk | 13885 | 7719 | 2066 |
| Survival estimate | 98% | 84% | 71% |
| Survival SE | 0.001 | 0.003 | 0.005 |
| PVI | | | |
| Number at risk | 23666 | 11316 | 1437 |
| Survival estimate | 97% | 79% | 68% |
| Survival SE | 0.001 | 0.003 | 0.005 |

**Figure 2**. Calibration curves for (A) the 30-day survival model and (B) 2-year survival model. Points are at predicted deciles of risk and the bars around points are 95% confidence intervals.

(A)




(B)

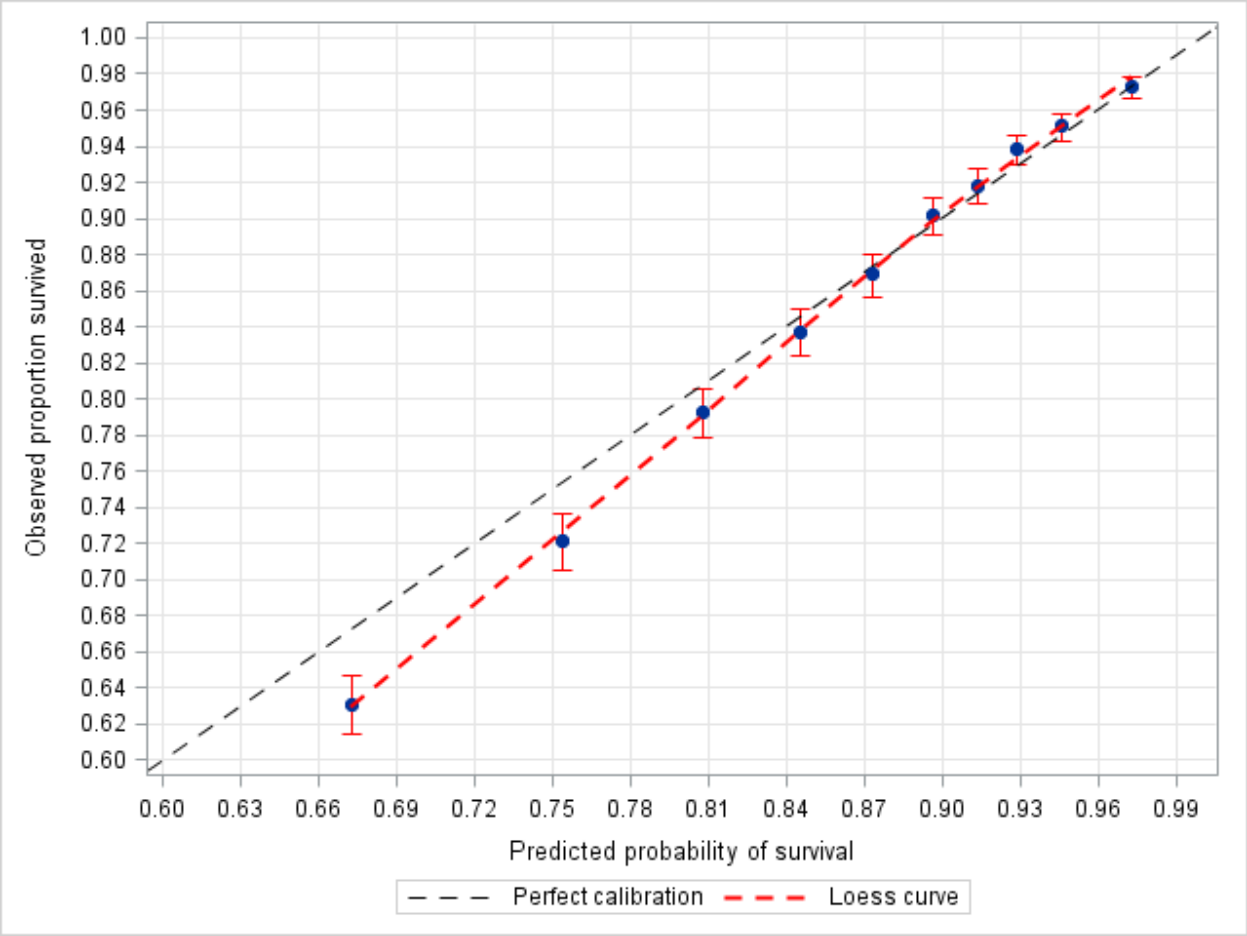

Observed proportion survived
1.00
0.98
0.96
0.94
0.92
0.90
0.88
0.86
0.84
0.82
0.80
0.78
0.76
0.74
0.72
0.70
0.68
0.66
0.64
0.62
0.60
0.60 0.63 0.66 0.69 0.72 0.75 0.78 0.81 0.84 0.87 0.90 0.93 0.96 0.99
Predicted probability of survival
Perfect calibration
Loess curve

**Figure 3.** Percentage of patients in each of three defined categories of risk: **low risk** (30-day survival >97% AND 2-year survival >70%), **medium risk** (30-day survival 95-97% and/or 2-year survival 50-70%), or **high risk** (30-day survival <95 or 2-year survival <50%).

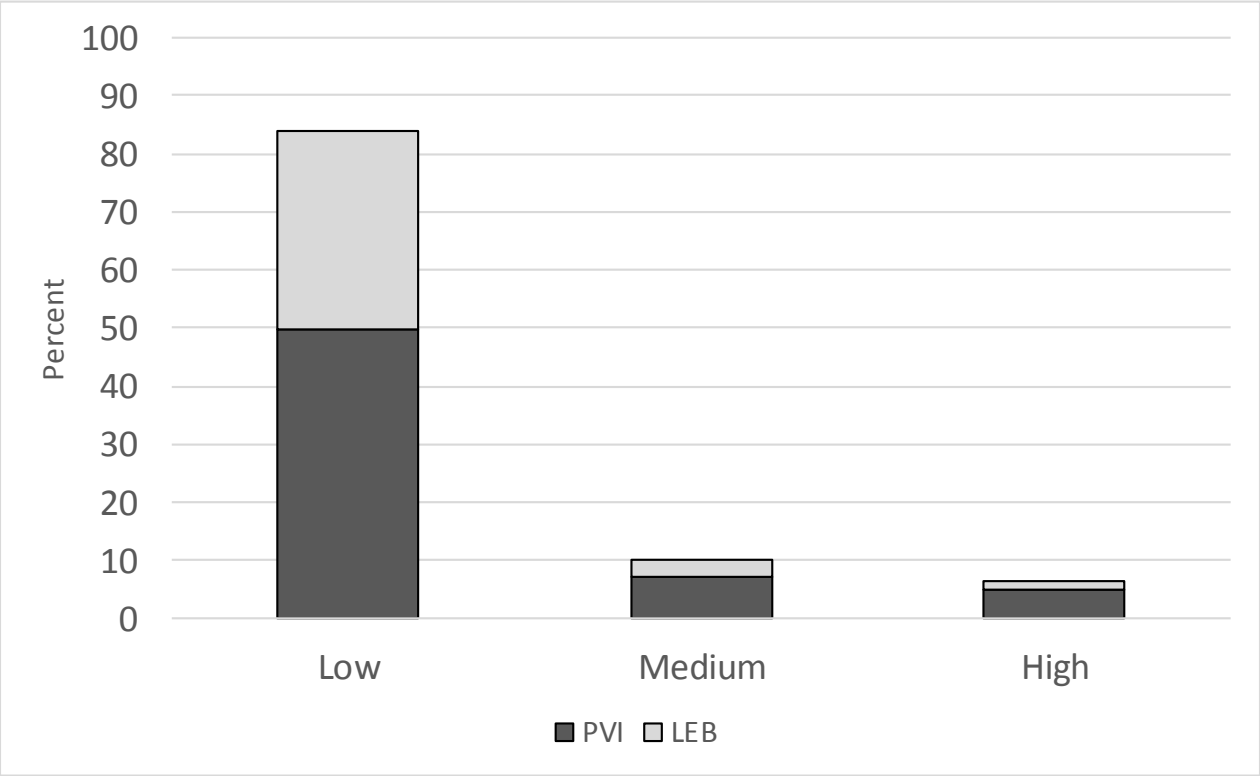
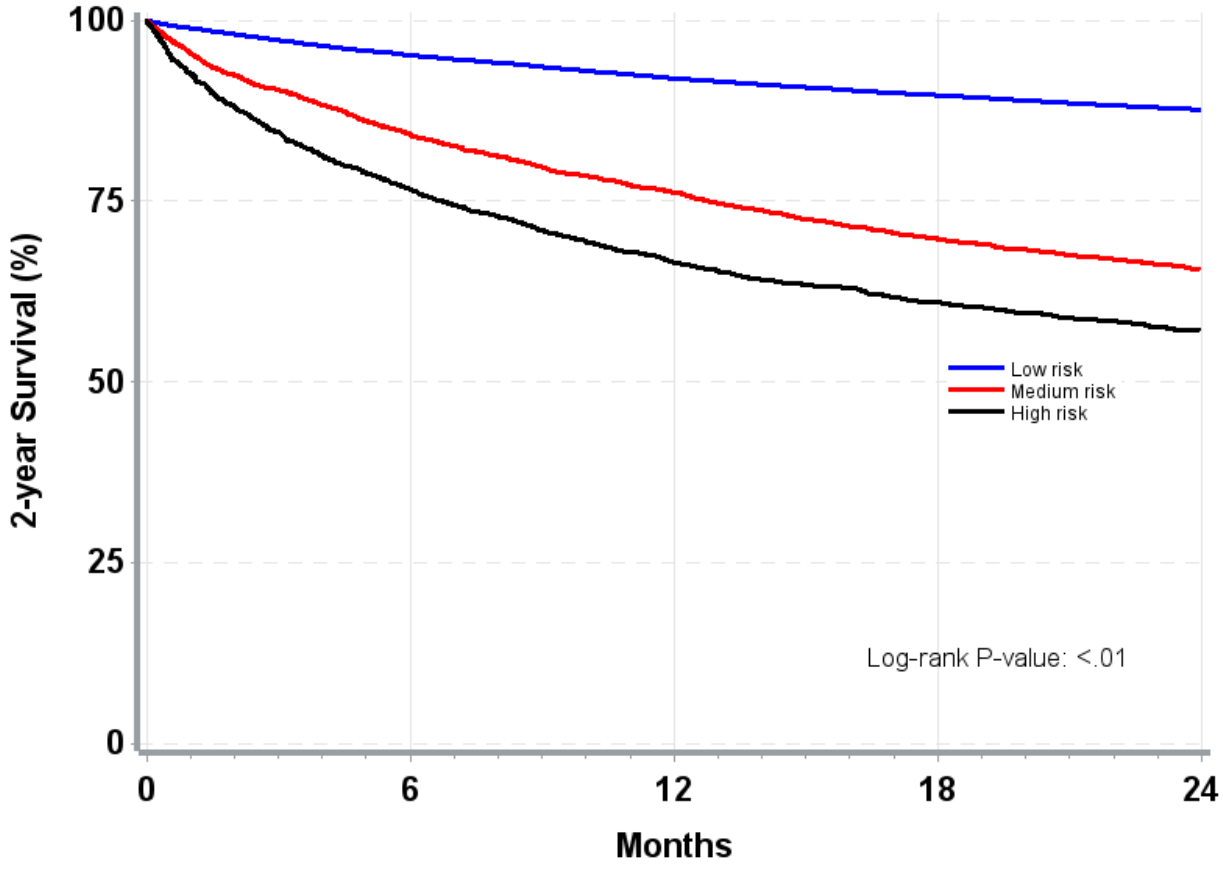


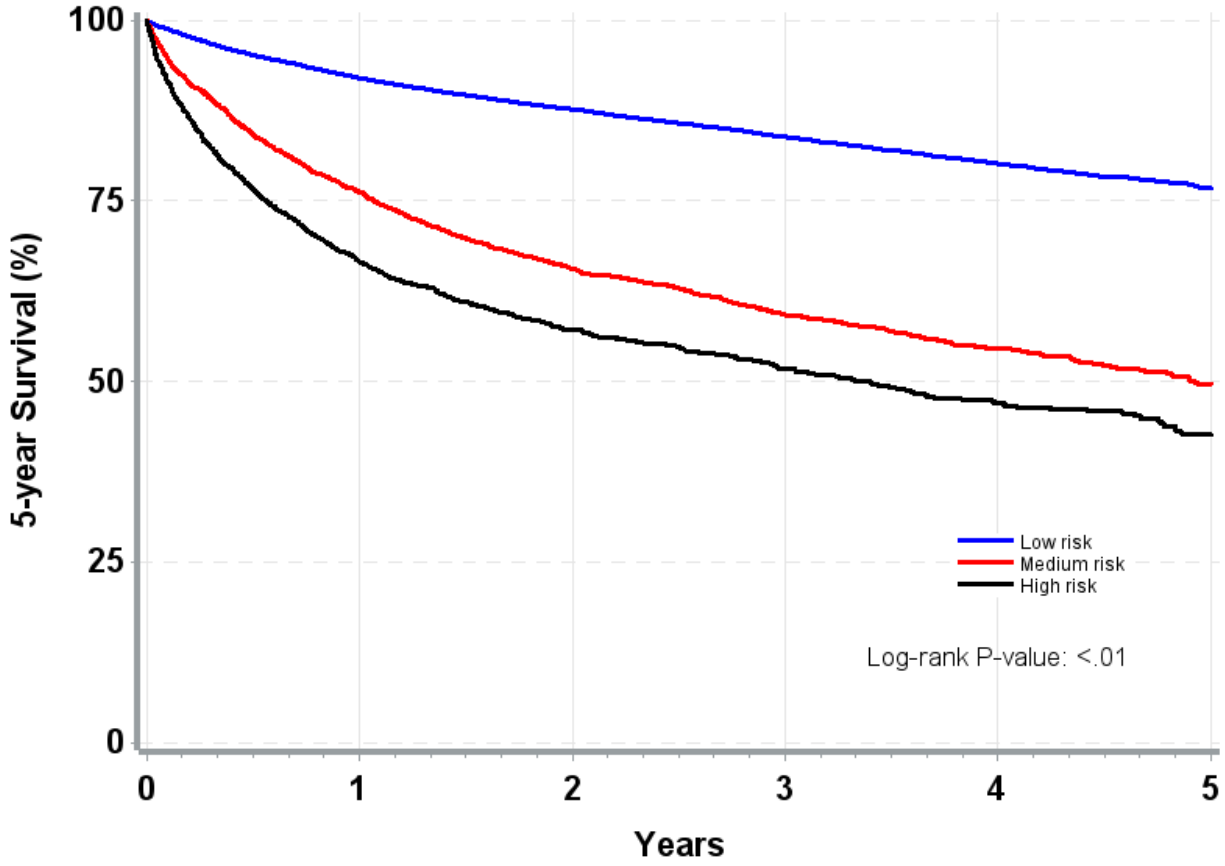
**Figure 4.** Kaplan Meier survival curve, stratified by risk group: (A) 2-year, and (B) 5-year.

(A)



| Months: | 1 | 6 | 12 | 24 |
|---|---|---|---|---|
| **Low risk** | | | | |
| Number at risk: | 27593 | 25777 | 21808 | 15172 |
| Survival estimate: | 0.99 | 0.95 | 0.92 | 0.88 |
| Survival SE: | 0.0006 | 0.0013 | 0.0017 | 0.0021 |
| **Medium risk** | | | | |
| Number at risk: | 3193 | 2753 | 2149 | 1306 |
| Survival estimate: | 0.95 | 0.84 | 0.76 | 0.66 |
| Survival SE: | 0.0036 | 0.0063 | 0.0075 | 0.0089 |
| **High risk** | | | | |
| Number at risk: | 2015 | 1628 | 1212 | 743 |
| Survival estimate: | 0.93 | 0.77 | 0.67 | 0.57 |
| Survival SE: | 0.0056 | 0.0091 | 0.0103 | 0.0114 |

**(B)**

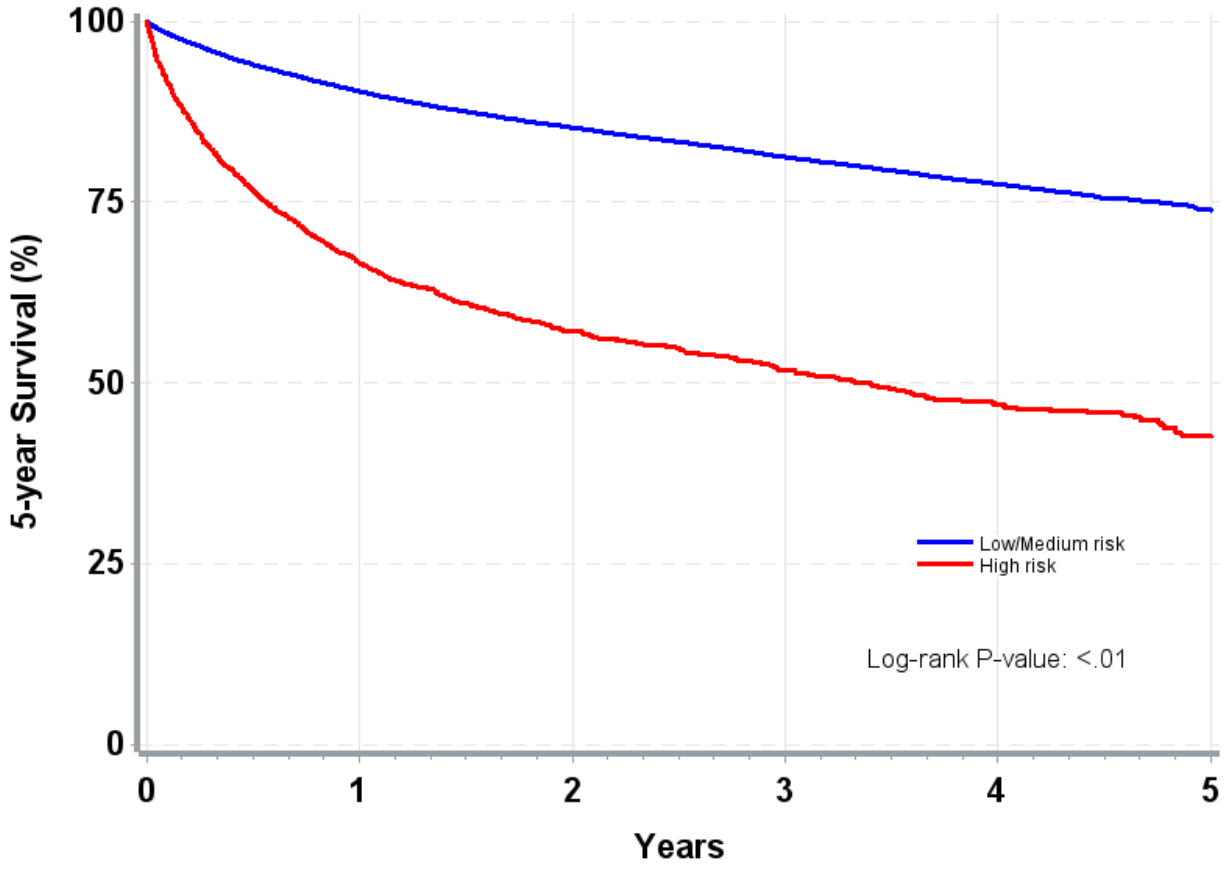



1

| Years: | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| **Low risk** | | | | | |
| Number at risk: | 21808 | 15172 | 9515 | 5522 | 2955 |
| Survival estimate: | 0.92 | 0.88 | 0.84 | 0.80 | 0.77 |
| Survival SE: | 0.0017 | 0.0021 | 0.0026 | 0.0032 | 0.0040 |
| **Medium risk** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Number at risk: | 2149 | 1306 | 752 | 412 | 192 |
| Survival estimate: | 0.76 | 0.66 | 0.59 | 0.55 | 0.50 |
| Survival SE: | 0.0075 | 0.0089 | 0.0101 | 0.0114 | 0.0139 |
| **High risk** | | | | | |
| Number at risk: | 1212 | 743 | 437 | 223 | 101 |
| Survival estimate: | 0.67 | 0.57 | 0.52 | 0.47 | 0.43 |
| Survival SE: | 0.0103 | 0.0114 | 0.0124 | 0.0139 | 0.0170 |

**Figure 5.** 5-year Kaplan Meier survival curve, stratified by risk group dichotomized as high risk versus medium/low risk.




| Years: | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| **Low/medium risk** | | | | | | |
| Number at risk: | 31298 | 23957 | 16478 | 10267 | 5934 | 3147 |
| Survival estimate: | 0.9997 | 0.90 | 0.85 | 0.81 | 0.77 | 0.74 |
| Survival SE: | 0.0001 | 0.002 | 0.002 | 0.003 | 0.003 | 0.004 |
| **High risk** | | | | | | |
| Number at risk: | 2176 | 1212 | 743 | 437 | 223 | 101 |
| Survival estimate: | 0.999 | 0.67 | 0.57 | 0.52 | 0.47 | 0.43 |
| Survival SE: | 0.0008 | 0.0103 | 0.0114 | 0.0124 | 0.0139 | 0.0170 |

**Figure 6. Potential interactive practice guideline mobile application.**

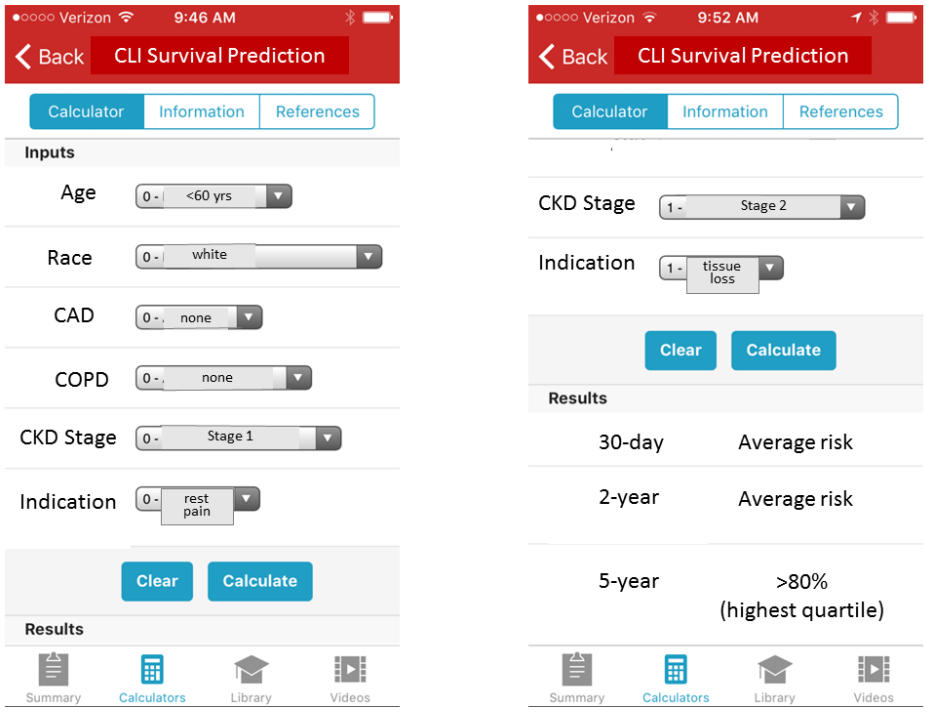


**Table 1.** Published survival data after revascularization for chronic limb threatening ischemia (CLTI).

| Study | Year of Publication | Cohort | Endpoint |
|---|---|---|---|
| Baubeta Fridh, E., et al.[1] | 2017 | Swedish registry with 10,617 patients revascularized open or endovascularly | 60% amputation-free survival by 2 years postoperatively |
| Iida, O., et al.[2] | 2015 | Japanese registry (OLIVE) with 314 patients revascularized endovascularly | 64% survival by 2 years postoperatively |
| Zeller, T., et al.[3] | 2014 | Randomized trial (IN.PACT DEEP) with 338 patients revascularized endovascularly | 90% survival by 1 year postoperatively |
| Conte, M.S., et al.[4] | 2006 | Randomized trial (PREVENT III) of edifoligide in 1404 patients revascularized open | 84% survival by 1 year postoperatively |
| Adam, D.J., et al.[5] | 2005 | Randomized trial (BASIL) in 452 patients revascularized open or endovascularly | 70% survival by 2 years postoperatively |
| Gruppo di Studio dell'Ischemia Cronica Critica degli Arti Inferiori[6] | 1997 | Italian registry of 522 patients | 70% survival by 2 years |

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**Table 2. Characteristics of chronic limb threatening ischemia patients (n=38470) in the VQI infrainguinal lower extremity bypass (LEB) and peripheral vascular intervention (PVI) cohorts, 2003-2017.** P-value for all comparisons was <.0001.

| | **TOTAL** | LEB | PVI |
|---|---|---|---|
| | **(n=38470)** | (n=14256) | (n=24214) |
| **Age** | | | |
| <60 years | **8400 (22)** | 3437 (24) | 4963 (21) |
| 60-70 years | **12105 (31)** | 4928 (35) | 7177 (30) |
| 71-80 years | **10030 (26)** | 3763 (26) | 6267 (26) |
| >80 years | **7935 (21)** | 2128 (15) | 5807 (24) |
| **Sex, male** | **23533 (61)** | 9432 (66) | 14101 (58) |
| **Race** | | | |
| White | **29061 (76)** | 11407 (80) | 17654 (73) |
| Non-white | **9376 (24)** | 2826 (20) | 6550 (27) |
| **Pre-Operative Factors** | | | |
| **Indication** | | | |
| Rest pain | **11674 (30)** | 5564 (39) | 6110 (25) |
| Tissue loss | **26796 (70)** | 8692 (61) | 18104 (75) |
| **Smoking status** | | | |
| Never | **11368 (30)** | 2751 (19) | 8617 (36) |
| Prior history | **15621 (41)** | 5962 (42) | 9659 (40) |
| Current | **11412 (30)** | 5528 (39) | 5884 (24) |
| **Hypertension** | **34577 (90)** | 12695 (89) | 21882 (90) |
| **CAD** | | | |
| None | **26715 (70)** | 9638 (68) | 17077 (71) |
| History of MI, asymptomatic or stable angina | **10799 (28)** | 4289 (30) | 6510 (27) |
| Unstable angina/MI within 6 months | **916 (2.4)** | 313 (2.2) | 603 (2.5) |
| **CHF** | **8888 (23)** | 2748 (19) | 6140 (25) |
| **Diabetes Mellitus** | **24328 (63)** | 7974 (56) | 16354 (68) |
| **COPD** | | | |
| Not treated or on meds | **7670 (20)** | 3293 (23) | 4377 (18) |
| Home oxygen | **1034 (2.7)** | 359 (2.5) | 675 (2.8) |
| **Chronic kidney disease stage** | | | |
| Stage 1: GFR ≥ 90 ml/min/1.73 m2 | **7295 (22)** | 3589 (27) | 3706 (18) |
| Stage 2: GFR 60 - 89 | **12597 (37)** | 5059 (39) | 7538 (37) |
| Stage 3: GFR 30 - 59 | **11506 (34)** | 3744 (29) | 7762 (38) |
| Stage 4: GFR 15 - 29 | **1949 (5.8)** | 599 (4.6) | 1350 (6.6) |
| Stage 5: GFR < 15 | **303 (0.9)** | 88 (0.67) | 215 (1.05) |

| | | | |
|---|---|---|---|
| **Previous ipsilateral revascularization** | **15066 (39)** | 7109 (50) | 7957 (33) |
| **Major amputation** | **2799 (7.3)** | 881 (6.2) | 1918 (7.9) |
| **Ambulation status** | | | |
| Independent | **24576 (64)** | 9725 (69) | 14851 (61) |
| With assistance | **10066 (26)** | 3489 (25) | 6577 (27) |
| Wheelchair-bound | **3266 (8.5)** | 881 (6.2) | 2385 (9.9) |
| Bedbound | **428 (1.1)** | 83 (0.59) | 345 (1.4) |
| **Preoperative medications** | | | |
| Beta blocker | **23353 (61)** | 8925 (63) | 14428 (60) |
| Antiplatelet | **29029 (75)** | 10940 (77) | 18089 (75) |
| Statin | **25264 (66)** | 9815 (69) | 15449 (64) |

1

2

**Table 3A. Adjusted model for 30-day survival (n=33486 with 606 deaths) among CLTI patients in VQI.** c-index = 0.76

| COVARIATES | HR (95%CI) | Beta Coefficient | p-value |
|---|---|---|---|
| Age, y | | | |
| <60 (referent) | | | |
| 60-70 | 1.7 (1.1, 2.4) | 0.51 | 0.01 |
| 71-80 | 2.6 (1.8, 3.8) | 0.97 | <.0001 |
| >80 | 4.5 (3.1, 6.5) | 1.5 | <.0001 |
| Race | | | |
| White (referent) | | | |
| Non-white | 0.69 (0.54, 0.87) | -0.38 | 0.002 |
| Pre-Operative Factors | | | |
| Indication | | | |
| Rest pain (referent) | | | |
| Tissue loss | 1.5 (1.2, 1.9) | 0.42 | <.0001 |
| CAD | | | |
| None (referent) | | | |
| History of MI, asymptomatic or stable angina | 1.3 (1.1, 1.5) | 0.25 | 0.0052 |
| Unstable angina/MI within 6 months | 2.2 (1.5, 3.2) | 0.78 | <.0001 |
| CHF | 1.7 (1.4, 2) | 0.53 | <.0001 |
| COPD | | | |
| None (referent) | | | |
| Not treated or on meds | 1.3 (1.1, 1.6) | 0.27 | 0.006 |
| Home oxygen | 2.4 (1.7, 3.2) | 0.86 | <.0001 |
| Chronic kidney disease stage | | | |
| Stage 1: GFR ≥ 90 ml/min/1.73 m2 (referent) | | | |
| Stage 2: GFR 60 - 89 | 0.95 (0.7, 1.31) | -0.05 | 0.76 |
| Stage 3: GFR 30 - 59 | 1.3 (0.95, 1.8) | 0.26 | 0.11 |
| Stage 4: GFR 15 - 29 | 2.1 (1.5, 3.1) | 0.76 | <.0001 |
| Stage 5: GFR < 15 | 4.3 (2.5, 7.2) | 1.45 | <.0001 |
| Ambulation status | | | |
| Independent (Referent) | | | |
| With assistance | 1.5 (1.3, 1.8) | 0.41 | <.0001 |
| Wheelchair-bound | 1.8 (1.4, 2.3) | 0.60 | <.0001 |
| Bedbound | 3.8 (2.5, 5.8) | 1.34 | <.0001 |
| Preop medications | | | |
| Statin | 0.75 (0.64, 0.89) | -0.29 | 0.001 |

Began with a model including all variables from univariate analysis that had a p-value < 0.01. The variables that were then eliminated one at a time when p>0.01 were: smoking, gender, and beta blocker use.

**Table 3B. Adjusted model of 2-year survival (n=33426 with 4913 deaths); c-index=0.72.**

| COVARIATES | HR (95%CI) | Beta Coefficient | p-value |
|---|---|---|---|
| Age, y | | | |
| <60 (referent) | | | |
| 60-70 | 1.4 (1.2, 1.5) | 0.32 | <.0001 |
| 71-80 | 2.0 (1.8, 2.2) | 0.68 | <.0001 |
| >80 | 3.2 (2.9, 3.6) | 1.17 | <.0001 |
| Race | | | |
| White (referent) | | | |
| Non-white | 0.78 (0.72, 0.84) | -0.25 | <.0001 |
| Preoperative Factors | | | |
| Indication | | | |
| Rest pain (referent) | | | |
| Tissue loss | 1.5 (1.4, 1.7) | 0.43 | 0.01 |
| Smoking status | | | |
| Prior history | 1.09 (1.02, 1.17) | 0.09 | 0.0003 |
| Current | 1.12 (1.02, 1.22) | 0.11 | <.0001 |
| CAD | | | |
| None (referent) | | | |
| History of MI, asymptomatic or stable angina | 1.2 (1.1, 1.3) | 0.18 | <.0001 |
| Unstable angina/MI within 6 months | 1.4 (1.2, 1.6) | 0.31 | 0.0003 |
| CHF | 1.6 (1.5, 1.7) | 0.49 | <.0001 |
| COPD | | | |
| None (referent) | | | |
| Not treated or on meds | 1.3 (1.2, 1.4) | 0.24 | <.0001 |
| Home oxygen | 1.7 (1.5, 1.9) | 0.52 | <.0001 |
| Chronic kidney disease stage | | | |
| Stage 1: GFR ≥ 90 ml/min/1.73 m2 (referent) | | | |
| Stage 2: GFR 60 - 89 | 1.02 (0.92, 1.13) | 0.02 | 0.67 |
| Stage 3: GFR 30 - 59 | 1.2 (1.1, 1.4) | 0.22 | <.0001 |
| Stage 4: GFR 15 - 29 | 1.9 (1.7, 2.2) | 0.64 | <.0001 |
| Stage 5: GFR < 15 | 3.0 (2.4, 3.7) | 1.09 | <.0001 |
| Ambulation status | | | |
| Independent (Referent) | | | |
| With assistance | 1.4 (1.3, 1.5) | 0.33 | <.0001 |
| Wheelchair-bound | 1.7 (1.5, 1.8) | 0.52 | <.0001 |
| Bedbound | 2.5 (2.1, 3.0) | 0.91 | <.0001 |

| | | | |
|---|---|---|---|
| Preoperative medications | | | |
| Beta blocker | 1.1 (1.1, 1.2) | 0.12 | 0.0002 |
| Antiplatelet | 0.88 (0.82, 0.94) | -0.13 | <.0001 |
| Statin | 0.83 (0.78, 0.88) | 0.12 | 0.0002 |

Began with a model including all variables from univariate analysis that had a p-value < 0.01. The variables that were then eliminated one at a time when p>0.01 were: history of major amputation, previous ipsilateral revascularization, hypertension, and diabetes mellitus.

**Table 3C. Adjusted model of 5-year survival (n=33423 with 6250 deaths);** c-index = 0.71.

| COVARIATES | HR (95%CI) | Beta Coefficient | p-value |
|---|---|---|---|
| Age, y | | | |
| <60 (referent) | | | |
| 60-70 | 1.3 (1.2, 1.4) | 0.27 | <.0001 |
| 71-80 | 1.9 (1.7, 2.0) | 0.62 | <.0001 |
| >80 | 2.9 (2.6, 3.2) | 1.07 | <.0001 |
| Race | | | |
| White (referent) | | | |
| Non-white | 0.76 (0.71, 0.81) | -0.28 | <.0001 |
| **Preoperative Factors** | | | |
| Indication | | | |
| Rest pain (referent) | | | |
| Tissue loss | 1.5 (1.4, 1.6) | 0.39 | <.0001 |
| Smoking status | | | |
| Never (referent) | | | |
| Prior history | 1.1 (1.04, 1.17) | 0.10 | 0.002 |
| Current | 1.17 (1.09, 1.27) | 0.16 | <.0001 |
| CAD | | | |
| None (referent) | | | |
| History of MI, asymptomatic or stable angina | 1.2 (1.1, 1.3) | 0.17 | <.0001 |
| Unstable angina/MI within 6 months | 1.3 (1.1, 1.5) | 0.27 | 0.0004 |
| CHF | 1.5 (1.5, 1.6) | 0.43 | <.0001 |
| Diabetes Mellitus | 1.07 (1.01, 1.13) | 0.06 | 0.03 |
| COPD | | | |
| None (referent) | | | |
| Not treated or on meds | 1.3 (1.2, 1.4) | 0.26 | <.0001 |
| Home oxygen | 1.7 (1.5, 1.9) | 0.52 | <.0001 |
| Chronic kidney disease stage | | | |
| Stage 1: GFR ≥ 90 ml/min/1.73 m2 (referent) | | | |
| Stage 2: GFR 60 - 89 | 1.04 (0.95, 1.14) | 0.04 | 0.37 |
| Stage 3: GFR 30 - 59 | 1.3 (1.2, 1.4) | 0.23 | <.0001 |

| | | | |
|---|---|---|---|
| Stage 4: GFR 15 - 29 | 1.9 (1.7, 2.1) | 0.62 | <.0001 |
| Stage 5: GFR < 15 | 3.0 (2.5, 3.6) | 1.09 | <.0001 |
| Ambulation status | | | |
| Independent (Referent) | | | |
| With assistance | 1.3 (1.3, 1.4) | 0.28 | <.0001 |
| Wheelchair-bound | 1.5 (1.4, 1.7) | 0.42 | <.0001 |
| Bedbound | 2.3 (1.9, 2.7) | 0.83 | <.0001 |
| **Preoperative medications** | | | |
| Beta blocker | 1.2 (1.1, 1.2) | 0.16 | <.0001 |
| Antiplatelet | 0.90 (0.84, 0.95) | -0.11 | 0.0002 |
| Statin | 0.82 (0.78, 0.87) | -0.20 | <.0001 |

Began with a model including all variables from univariate analysis that had a p-value < 0.01. The variables that were then eliminated one at a time when p>0.01 were: hypertension, history of major amputation, and previous ipsilateral revascularization.

**Table 4. Comparison of variables that remained significant in the adjusted survival models at 30 days, 2 years, and 5 years.**

| Factors | 30-day | 2-year | 5-year |
|---|---|---|---|
| Age, per decade | +++ | +++ | +++ |
| Chronic kidney disease stage | +++ | ++ | ++ |
| Ambulation status | +++ | ++ | ++ |
| COPD | ++ | + | + |
| CAD | + | + | + |
| CHF | + | + | + |
| Tissue loss (referent = rest pain) | + | + | + |
| Preoperative beta blocker | | + | + |
| Diabetes mellitus | | + | + |
| Smoking status | | | + |
| **Protective Factors:** | | | |
| Preoperative antiplatelet | | - | - |
| Preoperative statin | - | - | - |
| Non-white race | - | - | - |

+++ 3< highest hazard ratio <5
++ 2< highest hazard ratio <3
+ 1< highest hazard ratio <2
- 0.5< hazard ratio <1

**Table 5. Sample calculations using the survival prediction models.**

| Example | 30-day model | 2-year model | Composite model |
|---|---|---|---|
| 80-year-old white male diabetic with Stage 5 CKD and tissue loss.<br>- Ambulation status: independent<br>- Preoperative medications include:<br>statin, betablocker, antiplatelet | MEDIUM<br>probability = 95% | MEDIUM<br>probability = 59% | MEDIUM |
| 73-year-old white female diabetic smoker with CAD and tissue loss.<br>- Ambulation status: independent<br>- Preoperative medications include:<br>statin, betablocker, antiplatelet | LOW<br>probability = 99% | LOW<br>probability = 87% | LOW |
| 65-year-old African American male with stage 3 CKD and rest pain.<br>- Ambulation status: independent<br>- Preoperative medications include:<br>statin, betablocker, antiplatelet | LOW<br>probability = 99% | LOW<br>probability = 94% | LOW |
| 65-year-old African American male diabetic with Stage 3 CKD and tissue loss.<br>- former smoker, with stable CAD and history of CHF<br>- Ambulation status: independent<br>- Preoperative medications include:<br>statin, betablocker, antiplatelet | LOW<br>probability = 99% | LOW<br>probability = 83% | LOW |