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DOI:

[10.1016/j.jvs.2018.08.169](https://doi.org/10.1016/j.jvs.2018.08.169)

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Document Version

Peer reviewed version

Citation for published version (Harvard):

Simons, JP, Schanzer, A, Flahive, JM, Osborne, NH, Mills, JL, Bradbury, AW & Conte, MS 2019, 'Survival prediction in patients with chronic limb-threatening ischemia who undergo infrainguinal revascularization', *Journal of Vascular Surgery*, vol. 69, no. 6, supplement, pp. 137S-151S.e3. <https://doi.org/10.1016/j.jvs.2018.08.169>

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Checked for eligibility: 07/12/2018.

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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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Keywords: chronic limb threatening ischemia, survival, Vascular Quality Initiative

1 ABSTRACT

2 Objectives:

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

8 Methods:

9 The Vascular Quality Initiative was interrogated for patients who underwent infrainguinal bypass
10 or endovascular intervention for CLTI (1/2003-2/2017). Cox survival models were generated
11 using only pre-operative variables. Survival at 30 days, 2 years and 5 years was modeled
12 separately. Patients were defined as low-risk (30-day survival >97% and 2-year survival >70%),
13 medium-risk (30-day survival 95-97% or 2-year survival 50-70%), or high-risk (30-day survival
14 <95% or 2-year survival <50%).

15 Results:

16 Among 38,470 unique CLTI patients, 63% (n=24,214) underwent endovascular intervention and
17 37% (n=14,256) underwent infrainguinal bypass. Kaplan-Meier estimates of overall survival at
18 30 days, 2 years, and 5 years were 98%, 81%, and 69%, respectively. The proportion of patients
19 in the low-, medium-, and high-risk groups was 84%, 10%, and 6.5%, respectively. Patients in
20 the low-risk group were significantly less likely to undergo endovascular intervention compared
21 to those in the high-risk group (low-risk, 59% endovascular; high-risk, 75% endovascular;
22 $p<.0001$). Independent predictors of death were similar in all three models, with greatest
23 magnitude of effect associated with age >80 years, oxygen-dependent chronic obstructive
24 pulmonary disease, Stage 5 chronic kidney disease, and bedbound status. The c-index for the 30-
25 day model, 2-year model, and 5-year model was 0.76, 0.72, and 0.71, respectively. Procedure
26 type (open or endovascular) was not significant in any models, and did not impact c-indices.

27 Conclusions:

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

1 INTRODUCTION

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

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

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

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

15

1 METHODS

2 **Study Cohort:** Prospectively collected data from the VQI database were retrospectively
3 reviewed to identify all patients who underwent peripheral vascular intervention (PVI) or
4 infrainguinal lower extremity bypass (LEB) between January 1, 2003 and February 1, 2017. The
5 VQI is a national cooperative quality improvement initiative developed to prospectively collect
6 data and outcomes for patients undergoing vascular surgical procedures. It is comprised of over
7 3000 physicians from >400 academic and community medical centers across the United States.
8 Details of this registry are available online (www.vascularqualityinitiative.org). Data are
9 physician-reported at the time of operation for all consecutive cases, and include preoperative,
10 intraoperative, and in-hospital postoperative details. Follow up data are entered at approximately
11 one year postoperatively. Date of death is cross-referenced with the Social Security Death Index
12 and Medicare Claims. All information is sent to a central data repository where it is aggregated
13 and audited. Research analysts are blinded to patient, surgeon, and hospital identity.

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

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

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

10

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

1 weight in kilograms (kg) was collected, and body mass index (BMI) calculated according to the
2 formula: $BMI = \text{weight (kg)} / [\text{height (m)}]^2$. History of previous coronary revascularization
3 included both coronary artery bypass graft and percutaneous coronary intervention. History of
4 previous ipsilateral revascularization included any ipsilateral arterial bypass or previous
5 peripheral vascular intervention. Previous major amputation included both above- and below-
6 knee operations. Information on functional status included preoperative ambulation status
7 (independent, with assistance, wheelchair-bound, or bedbound) and living situation (nursing
8 home, or at home/homeless). Information on the presence of infection, and characteristics of
9 ulceration were not available; tissue loss was categorized only as present or absent. While ankle-
10 brachial index and toe-brachial index are collected, they were found to be missing (both limbs) in
11 $>40\%$ ($n=15714$), and therefore these variables were not used in any of the models.

12

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

18

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

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

7

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

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

11

12

1 **RESULTS**

2 **Cohort characteristics.** Using the VQI database, 38,470 unique patients were identified
3 who underwent infra-inguinal revascularization for CLTI (**Table 2**). Of these, 24,214 underwent
4 PVI (63%), and 14,256 underwent LEB (37%). Revascularization was more commonly
5 performed for tissue loss than for rest pain in both groups (tissue loss: PVI, n=18,104, 75%;
6 LEB, n=8692, 61%). The cohort was predominantly white (n=29,061, 76%), male (n=23,533,
7 61%), and between the ages of 60 and 80 (n=22,135, 58%). While some traditional vascular risk
8 factors were common (70% (n=27,033) were former or current smokers, and 63% (n=24,328)
9 were diabetic), others were less so (31% (n=11,715) had any CAD). The majority (90%) of
10 patients were ambulatory (independent or with assistance); the PVI cohort included more
11 patients who were wheelchair- or bed-bound (11% in the PVI group, versus 6.8% in the LEB
12 group). Notably, 50% of LEB performed were in patients with a prior history of ipsilateral limb
13 revascularization (indication and nature of the pre-VQI procedure unknown).

14 The PVI database was added to VQI in 2008. There has been an increase in the
15 proportion of PVI: 67% PVI in the 2013-17 time period compared with 57% PVI in the 2008-
16 2012 time period.

17

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

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

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

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

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

1 0.36. Since this correlation is considered at the medium range for correlations, we elected to
2 keep these covariates in our final model.

3
4 **Internal validation of models.** All three models demonstrated acceptable discrimination,
5 with the following c-indices: 30-day, $c=0.76$, 2-year, $c=0.72$, and 5-year $c=0.71$. Sensitivity and
6 specificity of the 2-year survival model was 90.2% and 31%, respectively; therefore, the positive
7 predictive value is approximately 85%, meaning that 85% of the time that a patient is predicted
8 to survive 2 years, that prediction is accurate. The negative predictive value is 43%, meaning that
9 43% of the time that a patient is not predicted to survive 2 years, that prediction is accurate. All
10 three models demonstrated inadequate calibration on Hosmer-May goodness of fit testing, all
11 $p<0.05$. In order to better understand this, calibration tables according to deciles of risk were
12 constructed. For the 30-day survival model ($p=0.024$), the calibration table demonstrated that
13 those in the 9th decile of risk had more deaths observed than expected ($p=0.01$). The other
14 deciles of risk fit well with this model. For 2-year survival model ($p<0.0001$), the calibration
15 table showed that the model only fit well for the 4th, 5th, and 7th deciles of risk. For 5-year
16 survival model ($p<0.0001$), the calibration table showed that the model does not fit well for the
17 lowest and highest deciles of risk. Given that Hosmer-May testing may be overly sensitive in a
18 dataset of this size, calibration curves were generated, demonstrating where the models perform
19 best and the amount of deviation, graphically (**Figure 2**).

20
21 **Risk groups.** Most patients were in the low-risk group (84%); 10% were in the medium-
22 risk group, and 6.5% in the high-risk group (**Figure 3**). PVI was performed more commonly in

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

5
$$h(t, X) = h_0(t) \exp(\sum \beta_i x_i)$$
 where $X = (x_1, x_2, \dots, x_p)$ are the covariates, and $h_0(t)$ is the
 6 baseline hazard.

7 Beta coefficients are provided in Tables 3A and 3B; and samples calculations are
 8 provided in Table 5. Once the 30-day and 2-year probability of survival is calculated for each
 9 patient, we used 1 - probability of survival to get probability of mortality. When the 30-day
 10 probability of survival >0.97 and 2-year probability of survival >0.70 then patient is considered
 11 low risk. If (30-day probability of survival >0.97 and 2-year probability of survival >= 0.50 and
 12 2-year probability <=0.7) or (30-day probability of survival <=0.97 but >0.95 and 2-year
 13 probability of survival >=0.5) the patient is considered at medium risk. And high risk patients
 14 are those with (2-year survival probability <0.5 and any non-missing 30-day probability of
 15 survival) or (30-day survival probability <0.95 and any non-missing 2-year probability of
 16 survival).

17

18 Of those patients who were “high risk” (n=2176) based on the “30-day survival <95%”
 19 criterion, 37% (n=815) also met criteria based on the “2-year survival <50%” criterion. Among
 20 those patients who were “low risk” (n=27,952) based on the “30-day survival >97%” criterion,
 21 100% also met criteria based on the “2-year survival >70%” criterion. When separated out
 22 according to risk at the individual time-points (30-day survival risk, and 2-year survival risk

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

3 Kaplan Meier survival analysis, stratified by risk group demonstrated significant
4 differences when truncated at 2 years (log-rank, $p<0.01$), and when truncated at 5 years (log-
5 rank, $p<0.01$) (**Figure 4**). The 5-year survival estimates were: low-risk 77% (SE=0.004),
6 medium-risk 50% (SE=0.014), and high-risk 43% (SE=0.017).

7 Kaplan Meier survival analysis, stratified by risk group, but dichotomized into “high
8 risk” and “low/medium risk” were significantly different on log-rank analysis ($p<0.01$) (**Figure**
9 **5**).

10

1 DISCUSSION

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

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

1 Despite these favorable results in our cohort of CLTI patients, with most patients
2 classified as low-risk (84%), nearly 2/3 of the total cohort were treated using an endovascular
3 approach. These data mirror reports from other large registry studies, likely reflecting
4 considerations beyond survival estimation alone.(18, 19) Within each risk group, endovascular
5 intervention was used more commonly. However, the proportion of endovascular treatment rose
6 as risk group increased, with endovascular intervention used in 75% of high-risk patients,
7 compared with 59% in the low-risk group. Notably, the low-risk subgroup (comprising 84% of
8 all patients undergoing infra-inguinal revascularization for CLTI in the VQI database) enjoyed a
9 >75% survival out to five years. Given the significant recrudescence of foot ulcerations and
10 CLTI symptoms, durability of revascularization is likely to be an important consideration for
11 many such patients.

12

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

20

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

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

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

7 Other prediction models have been published to facilitate decision making in CLTI.(4,
8 13, 16, 17, 30-32) Many of these have used a composite endpoint of amputation-free survival
9 (AFS). AFS is an attractive endpoint for the treating provider, because it addresses both survival,
10 without which there cannot be treatment “success,” but also addresses limb salvage, which is the
11 surgeon’s goal of revascularization. However, these models have not performed particularly well
12 on external validations, perhaps due to the discrepancy between predictors of survival and
13 predictors of limb salvage. They have not gained widespread use in clinical practice, perhaps
14 because their direct impact on decision-making is unclear. Instead, they may be better suited to
15 benchmarking outcomes of revascularization.(16) The BASIL model was the only one that was
16 derived from a cohort of CLTI patients who underwent both endovascular and open
17 revascularization, but this was a highly selected group that met equipoise considerations by these
18 investigators and may not reflect contemporary practice. The model described herein offers the
19 advantage of being derived from a large, heterogeneous cohort, which may better represent real
20 world practice in the US. It is also focused on survival only, for which we may have increased
21 predictive ability, compared with the composite endpoint, AFS. The value of decisions tools such
22 as this rests in providing objective criteria, and relative weighting, to support clinical judgment
23 and increase evidence-based care of the vascular patient.

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

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

13

14 **CONCLUSION**

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

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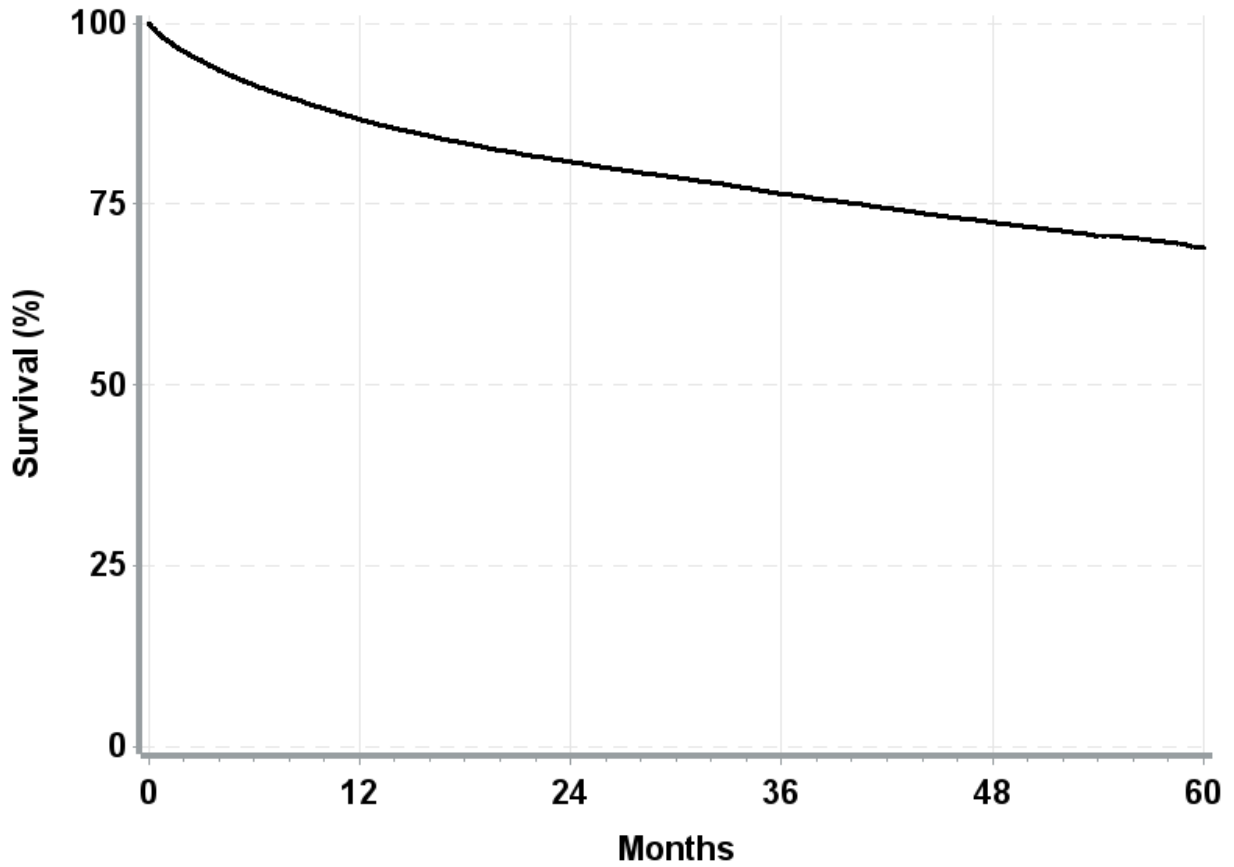
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14

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

4 A.



5

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

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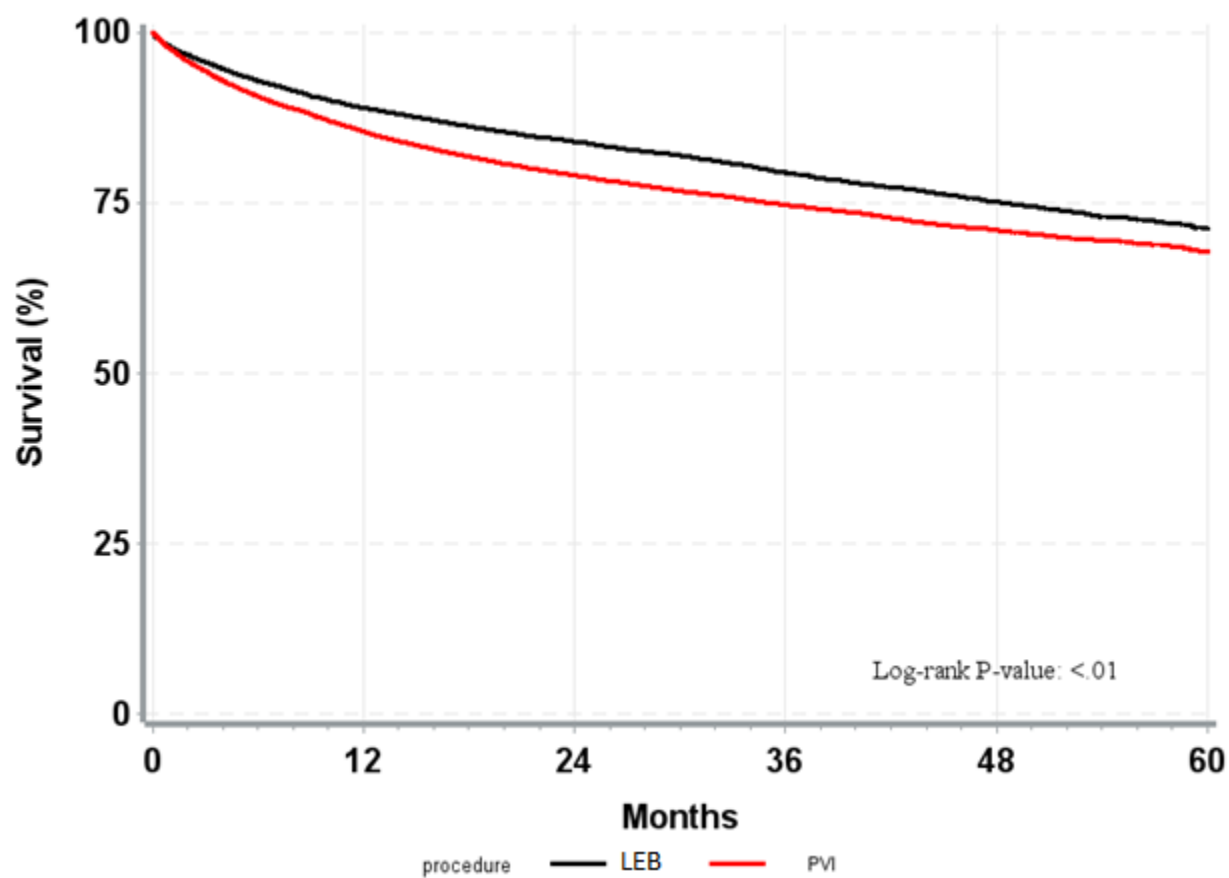
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1 B.



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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

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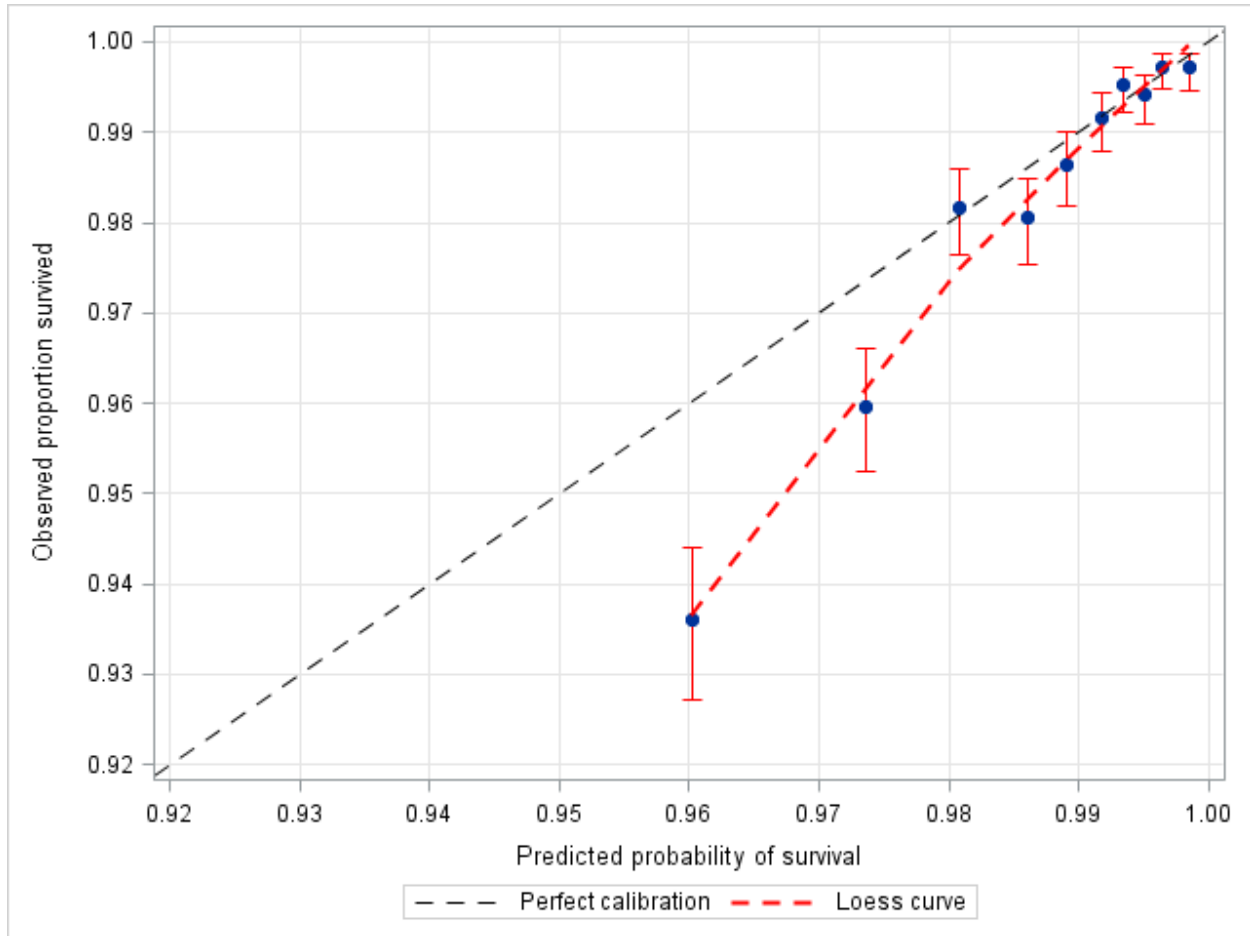
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1 **Figure 2.** Calibration curves for (A) the 30-day survival model and (B) 2-year survival model.
 2 Points are at predicted deciles of risk and the bars around points are 95% confidence intervals.

3

4 (A)

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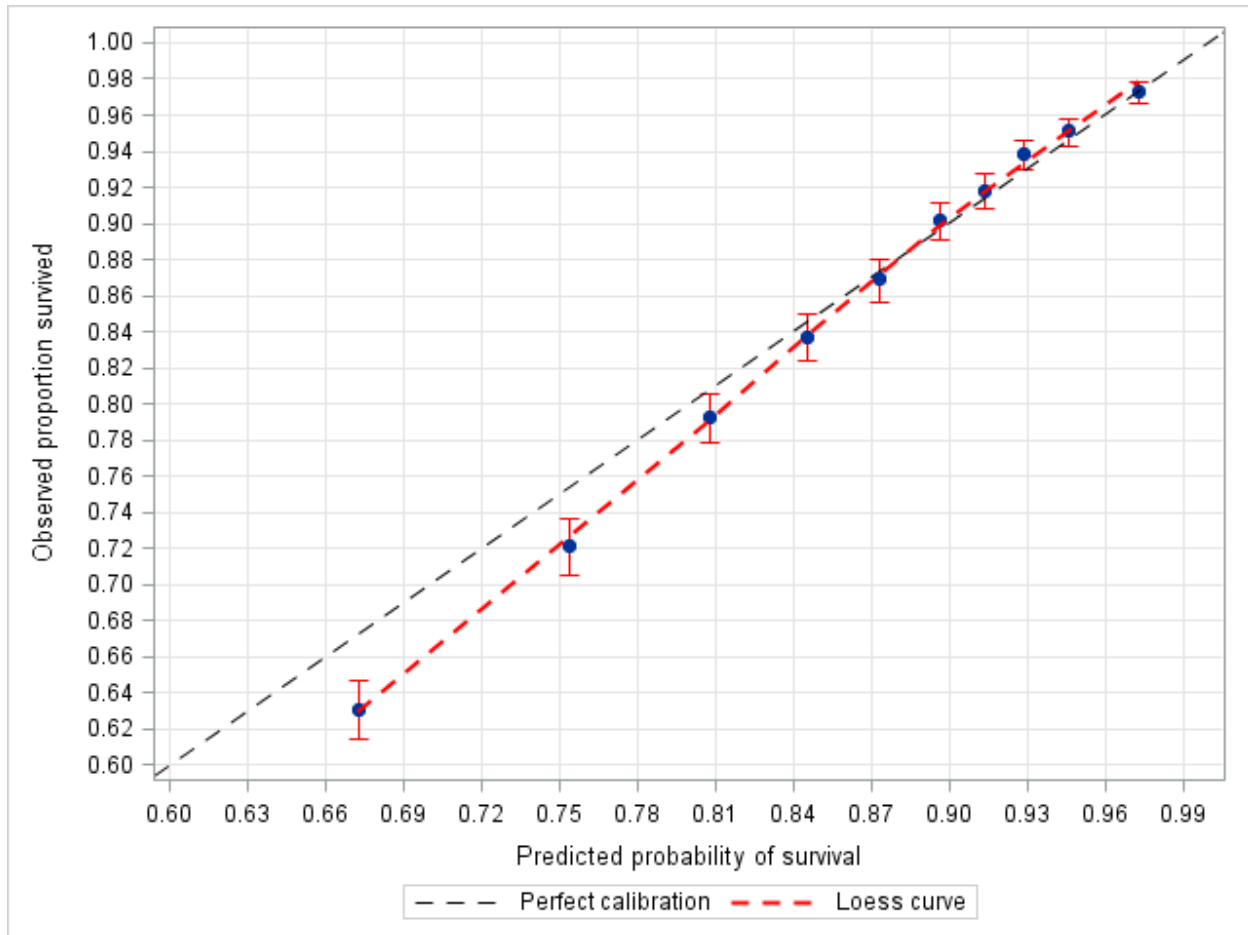
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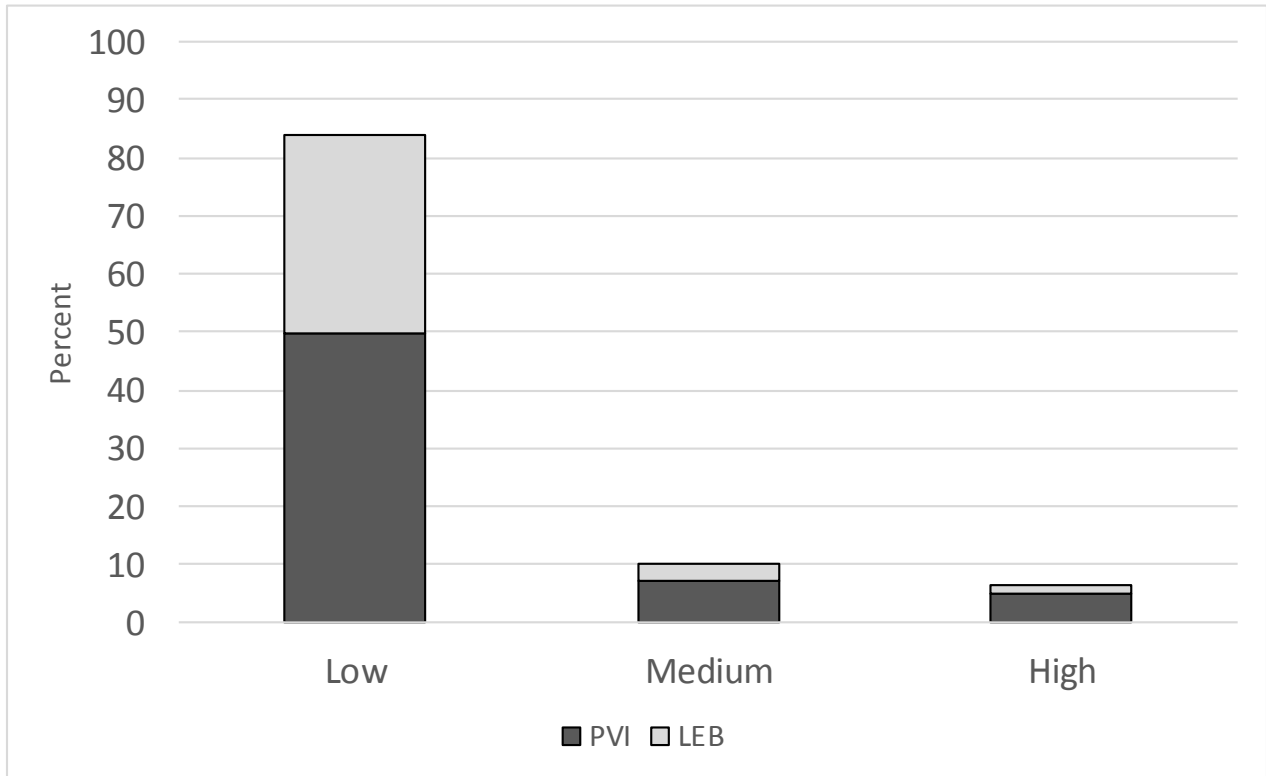
(B)



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

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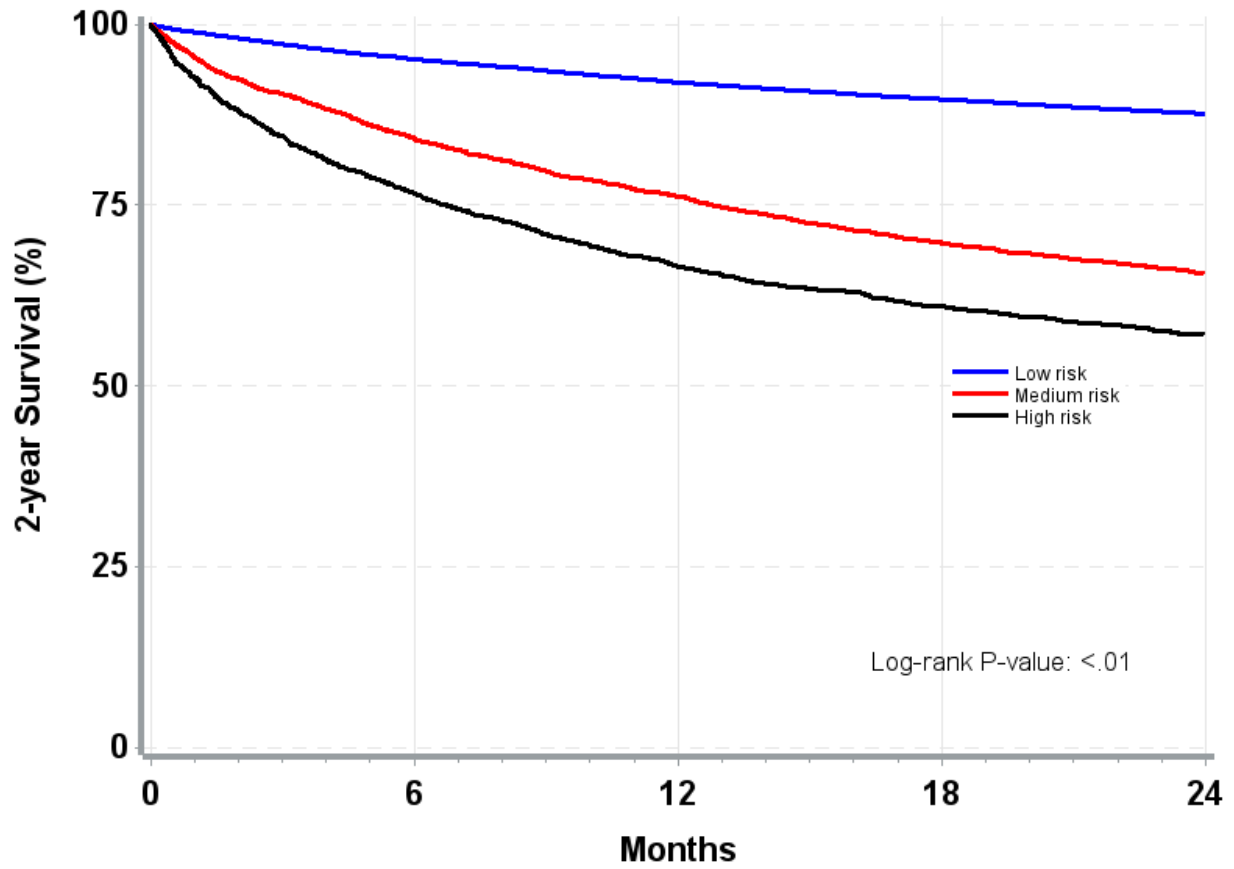
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1 **Figure 4.** Kaplan Meier survival curve, stratified by risk group: (A) 2-year, and (B) 5-year.

2 (A)



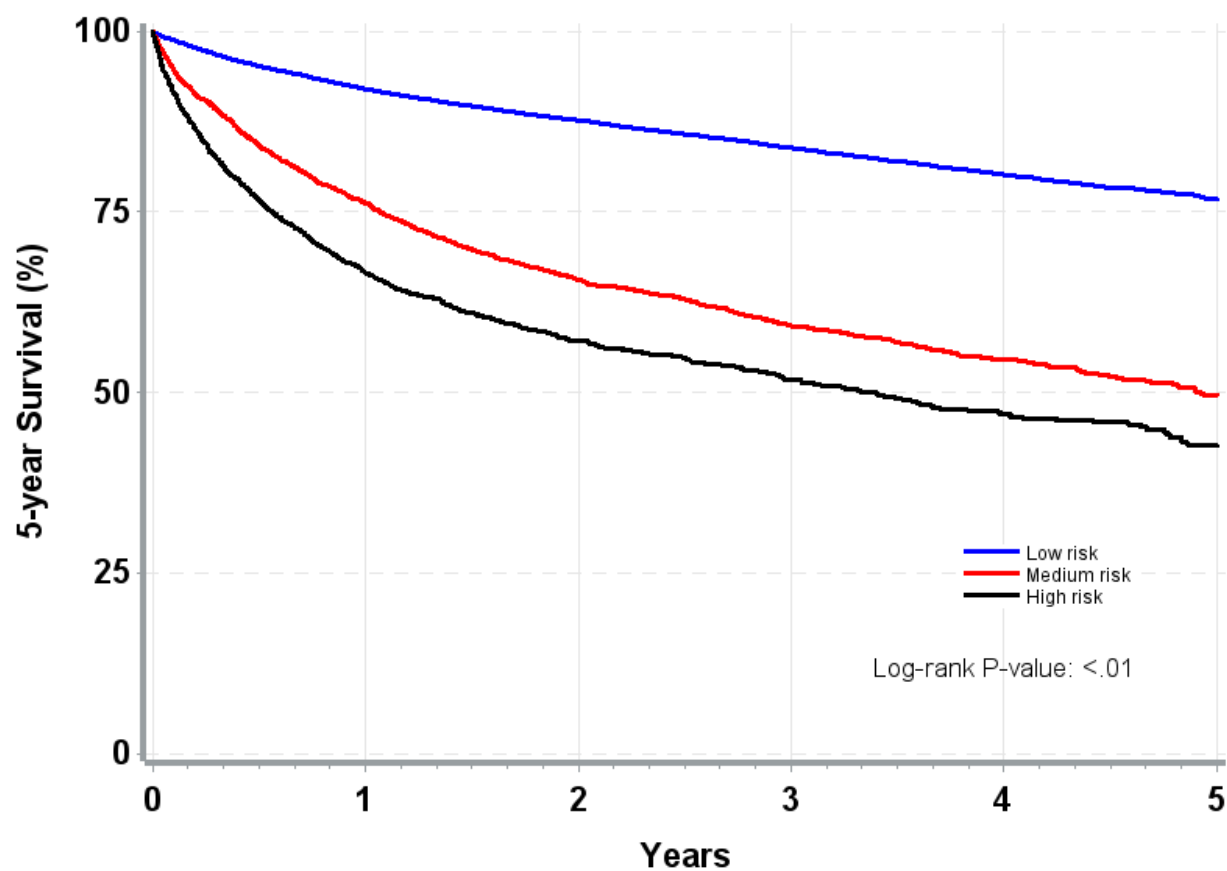
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Months:	1	6	12	24
Low risk				
Number at risk:	27593	25777	21808	15172
Survival estimate:	0.99	0.95	0.92	0.88
Survival SE:	0.0006	0.0013	0.0017	0.0021
Medium risk				
Number at risk:	3193	2753	2149	1306
Survival estimate:	0.95	0.84	0.76	0.66
Survival 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

1

2

3 **(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

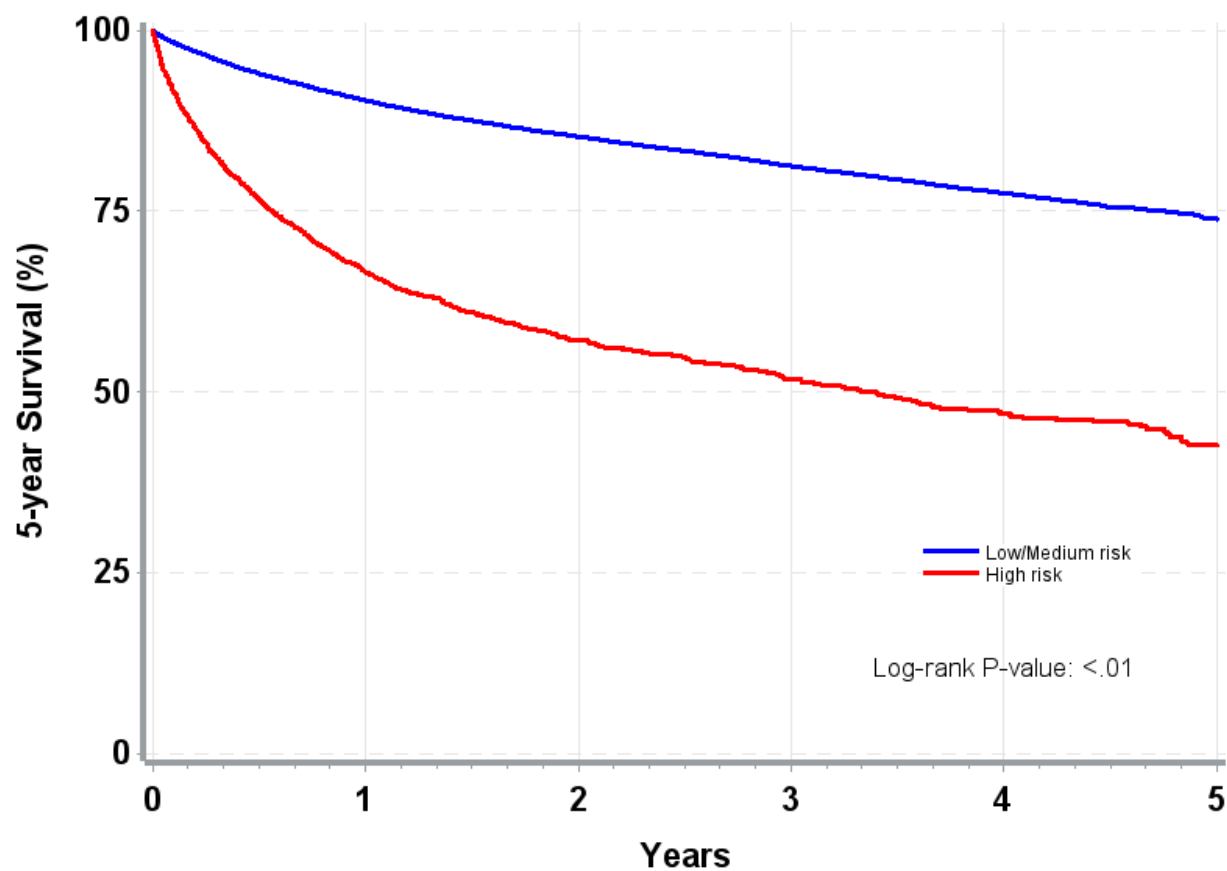
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- 1 **Figure 5.** 5-year Kaplan Meier survival curve, stratified by risk group dichotomized as high risk
 2 versus medium/low risk.



3

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

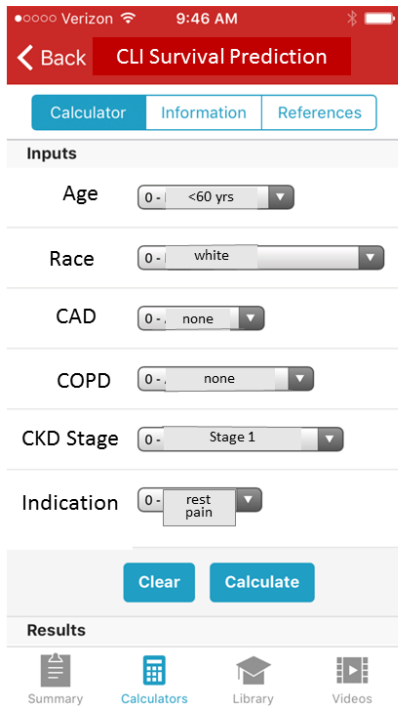
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1 **Figure 6. Potential interactive practice guideline mobile application.**

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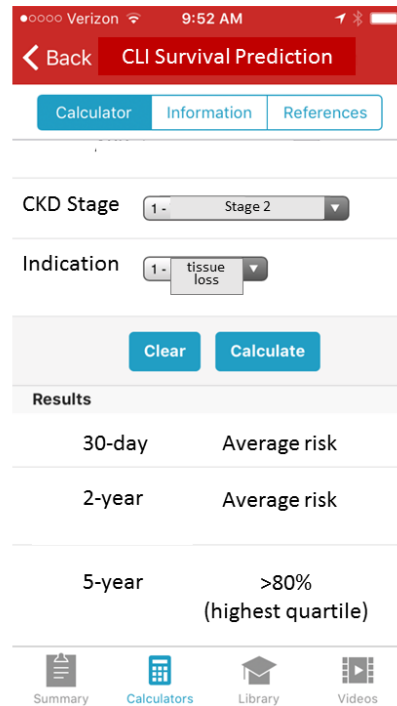
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1 **Table 1.** Published survival data after revascularization for chronic limb threatening ischemia
 2 (CLTI).

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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1 **Table 2. Characteristics of chronic limb threatening ischemia patients (n=38470) in the**
 2 **VQI infrainguinal lower extremity bypass (LEB) and peripheral vascular intervention**
 3 **(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 \geq 90 ml/min/1.73 m ²	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

1 **Table 3A. Adjusted model for 30-day survival (n=33486 with 606 deaths) among CLTI**
 2 **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 \geq 90 ml/min/1.73 m ² (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

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

1

2 **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 \geq 90 ml/min/1.73 m ² (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

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

4

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

COVARIATES	Beta	
	HR (95% CI)	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 \geq 90 ml/min/1.73 m ² (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

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

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1 **Table 4. Comparison of variables that remained significant in the adjusted survival models**
 2 **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 +++ 3< highest hazard ratio <5

4 ++ 2< highest hazard ratio <3

5 + 1< highest hazard ratio <2

6 - 0.5< hazard ratio <1

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

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