Title

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Endovascular First Treatment is Associated with Improved Amputation Free Survival in Patients with Critical Limb Ischemia

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Abstract

Background: Critical Limb Ischemia (CLI) remains a difficult disease to treat with limited level one data. The BEST-CLI trial is attempting to answer whether initial treatment with open surgical bypass or endovascular therapy improves outcomes, although it remains in enrollment. This study aims to compare amputation free survival (AFS) and reintervention rates in patients treated with initial open surgical bypass or endovascular intervention for ischemic ulcers of the lower extremities.

Methods and Results: Using California non-federal hospital data linked to statewide death data, all patients with lower extremity ulcers and a diagnosis of peripheral artery disease who underwent a revascularization procedure from 2005 to 2013 were identified. Propensity scores were formulated from baseline patient characteristics. Inverse probability weighting was used with Kaplan-Meier analysis to determine AFS and time to reintervention for open vs. endovascular treatment. Mixed effects Cox proportional hazards modeling was used to adjust for patient ability to manage their disease and hospital revascularization volume. A total of 16,800 patients were identified. Open surgical bypass was the initial treatment in 5,970 (36%) while 10,830 (64%) underwent endovascular interventions. Patients in the endovascular group were slightly younger compared to the open group (70 vs. 71 years, ± 12 years, $p<0.001$). Endovascular first patients were more likely to have co-morbid renal failure (36% vs. 24%), coronary artery disease (34% vs 32%), congestive heart failure (19% vs 15%), and diabetes mellitus (65% vs 58%, all p values <0.05). After inverse propensity weighting as well as adjustment for patient ability to manage their disease and hospital revascularization experience, open surgery first was associated with a worse AFS (HR 1.16, 95% Confidence Interval (CI): 1.13–1.20) with no difference in mortality (HR 0.94, 95% CI: 0.89–1.11). Endovascular first was associated with higher rates of reintervention (HR 1.19, 95% CI: 1.14–1.23).

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Disclosures:
None

Conclusions: Patients with CLI have multiple comorbidities and initial surgical bypass is associated with poorer AFS compared to an endovascular first approach perhaps due to increased severity of wounds at the time of presentation.

Subject Terms:

Peripheral Vascular Disease; Revascularization; Mortality/Survival; Quality and Outcomes

Keywords

Bypass; bypass surgery; endovascular; endovascular surgery; CLI; critical limb ischemia; amputation; amputation free survival; open surgery

Introduction:

The most severe form of peripheral artery disease (PAD) is Critical Limb Ischemia (CLI) which ranges from rest pain in the affected limb to extensive gangrene. With the aging population, the incidence of CLI has continued to rise and it is estimated that by the year 2050 the number of patients who undergo amputation is expected to more than double from 1.6 to 3.6 million.[1] The highest number of amputation is in patients who have combined limb ischemia and diabetes.[2] Risk factor modification is imperative as there is currently no medical treatment for CLI and the associated mortality is as high as 50% at one year.[3]

Historically, open surgical bypass has been the gold standard of treatment with excellent long term results.[4] In 2010, the Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial, which is the only randomized control trial to compare open to endovascular therapy, demonstrated no difference between the two strategies for patients surviving less than two years but a trend toward better amputation free survival (AFS) in those treated with open surgery first and surviving beyond two years.[5] Since the publication of the BASIL trial, the availability endovascular technology and enthusiasm for endovascular first therapy has significantly expanded. This is especially true given the decreased mortality and incidence of major adverse cardiovascular events with endovascular treatment.[6]

Currently, the BEST-CLI trial is attempting to answer whether initial treatment with open surgical bypass or endovascular therapy improves outcomes, however the trial remains in enrollment.[7] While the trial will be able to inform us on the outcomes for those patients who meet the inclusion criteria and are subsequently treated by physicians with expertise in the management of infra-inguinal disease, there will remain questions regarding what the outcomes are for all patients treated over a large variety of hospital settings. This study compares AFS, reintervention rates, and overall mortality in patients treated with initial open surgical bypass or endovascular intervention for CLI across all non-federal hospitals in California.

Methods:

This retrospective cohort was developed from all-payer statewide data obtained from California's Office of Statewide Health Planning and Development (OSHPD). The primary outcome was AFS among patients >18 years old with lower extremity (LE) ulcers and a diagnosis of PAD who presented to non-federal California hospitals from January 1, 2005 to December 31, 2013. The Institutional Review Boards for the California Health and Welfare Agency (Committee for the Protection of Human Subjects) approved this study and waived consent given the retrospective nature of the study. Because the dataset used in this study contains patient level information, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols must be obtained from OSHPD.

Database

The California OSHPD database consists of three subset databases, the PDD, EDD, and ASD. The Patient Discharge Database (PDD) captures all non-federal inpatient hospitalizations. In addition, OSHPD collects data from all emergency department visits in the Emergency Department Database (EDD) and from eligible ambulatory surgery centers in the Ambulatory Surgery Database (ASD) within California. Non-federal hospitals account for 96% of the hospitals in California. Records for each patient in the OSHPD database are linked through an encrypted Social Security number called the Record Linkage Number.[8, 9] Patients in the EDD dataset are those who are evaluated in the emergency room (ER) and sent home. Patients who are admitted from the ER are captured as part of the PDD. For each PDD visit, the collected data include demographic information, insurance status, a principal diagnosis code with up to 24 secondary diagnoses codes, a principal procedure code, and up to 20 additional secondary procedure codes. Within the PDD, medical diagnoses and procedures were coded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) through September 2015. Procedure data in the ASD database are coded using Current Procedural Terminology codes. Each patient encounter is also marked with a unique hospital identification number.

Patient Cohort

We created the index patient cohort by searching the PDD, EDD, and ASD data for principal and secondary ICD-9-CM diagnosis codes indicating the presence of a LE ulcer and a corresponding diagnosis of diabetes (DM), PAD, or combination of PAD/DM (Supplemental Table 1). Records with ICD-9-CM codes indicating an acquired arteriovenous fistula, rheumatic disease, or thromboangitis obliterans as the underlying arterial condition were excluded. For this specific project, patients with DM without PAD were excluded. Patients coded as having PAD and with a subsequent code for DM were included in the PAD/DM disease group. Because administrative data is primarily used for billing, many patients may not have the codes of interest as their principal diagnosis and could potentially be missed during cohort construction. To account for this, we created a comprehensive coding system within each disease group (PAD, DM, PAD/DM) based on a combination of the principal and 24 secondary diagnosis codes. This system was used to classify patients within each disease group for those admitted specifically due to the LE ulcer as opposed to those where the ulcer was identified while admitted to the hospital for another reason. Within the PAD disease group there were seven classes and the combination PAD/DM patients had eight classifications (Supplemental Figure 1). Patients less than 18 years old were excluded due to the low prevalence of LE ulcers resulting from these diseases.[2] We conducted a five year look back from the index diagnosis to identify any prior revascularization procedures and excluded those patients who had undergone previous revascularization procedures (Supplemental Table 2). Additionally, any patient who did not undergo a revascularization procedure as part of their treatment was also excluded. This resulted in a cohort of patients with CLI (PAD and wound code or PAD/DM and wound code) who underwent either endovascular first or open first therapy (Figure 1).

Comorbidity Data and Access Variables

The Elixhauser comorbidity[10] software was used to define comorbidities; DM and PAD were excluded from the list of comorbidities specified in this manner. We also captured additional comorbid conditions not included in the index, specifically coronary artery disease, chronic obstructive pulmonary disease, cerebrovascular disease, arrhythmias, and tobacco use.

As a proxy for the patients' ability to manage chronic diseases and their LE wound in the outpatient setting, we identified hospitalizations and ER visits in the 60 days prior to their first diagnosed wound encounter. This is an inverse relationship in which a higher utilization of ER visits or admissions associates with poorer ability to manage their chronic illnesses.[11] We will refer to this as "patient ability" throughout this study.

Hospital Revascularization Experience:

To determine the hospital experience with revascularizations, we examined the total number of open and endovascular revascularization procedures performed from 2005 to 2013. The total number was divided into the three categories. Low volume hospitals performed <50 procedures, medium volume centers performed 51 to 100, and high-volume centers performed >100 procedures.

Outcomes:

Our primary outcome was AFS which is defined as freedom from major amputation (below or above the knee) or death. Secondary outcomes were reintervention and all-cause mortality. The OSHPD data is linked to the California Death Statistic Master File which allows the tracking of out of hospital death of all patients who die within California or in states with a reciprocal reporting relationship with the state.[12] Reintervention was classified as any additional open or endovascular procedure performed after the index revascularization procedure.

Statistical Analysis:

Means and standard deviations were used to describe continuous variables. Frequencies and percentages are used for categorical variables. For non-parametric data, median and interquartile range (IQR) were reported. Continuous variables were compared using the Wilcoxon rank sum test and categorical values using χ^2 or Fisher exact tests. Unadjusted survival curves were estimated using the Kaplan-Meier method, and adjusted survival curves were estimated using inverse probability of treatment weighting (IPTW).[13] Mixed effects Cox proportional hazards modeling was used to determine the influence of "patient ability" and hospital revascularization experience on AFS, repeat intervention, and overall mortality. Because there was a violation of the proportional hazards assumption, the model was modified to include an interaction of the covariates with a function of time. Propensity scores were developed to adjust for covariates that may influence the decision for open versus endovascular therapy. The covariates included in the propensity model included: age, sex, race/ethnicity (Caucasian, African American, Hispanic, Asian, Other/Unknown), diabetes mellitus, coronary artery disease, renal failure, year of treatment, and insurance coverage. Diagnostic tests to demonstrate balance of the covariates after IPTW included calculation of the standardized difference before and after weighting and visual inspection of a kernel density plot to verify propensity score overlap between groups. Visual inspection of propensity scores by treatment group before weighting also demonstrated adequate overlap in the two cohorts.

Results:

From 2005 to 2013, over 102 million inpatient, ambulatory surgery, and ER visits were documented in non-federal California facilities (Figure 1). There were 250,433 patients who met the diagnosis criteria. Patients who had a prior amputation (n=8,870) or a prior revascularization (n=21,732) were excluded. Duplicate patients, those with missing gender and those with a date of death prior to the date of amputation, were also excluded to create a cohort of 219,547 unique patients with a first documented visit for a LE ulcer and a diagnosis of PAD, DM, or PAD/DM. After excluding 131,731 patients with DM but without PAD, 87,816 patients remained. Of these, 16,800 received an index open or endovascular procedure. Open surgical bypass was the initial treatment in 5,970 (36%) while 10,830 (64%) underwent endovascular first interventions.

Men represented 59% of the overall cohort, being equal in both groups. Patients in the endovascular first group were slightly younger compared to the open first group (70 vs. 72 years, standard deviation (SD) ± 12 years, $p<0.001$, Table 1). Forty-eight percent of the overall cohort was Caucasian, 25% was Hispanic, 10% was African American, 6% was Asian, and 11% was classified as Other or Unknown. Caucasian patients were more likely to have open surgery first, whereas Hispanic patients were more likely to undergo endovascular treatment first. The endovascular-first patients had more comorbidities with higher rates of renal failure (36% vs. 24%), coronary artery disease (34% vs 32%), congestive heart failure (19% vs 15%), and diabetes mellitus (65% vs 58%, all p values <0.05) than the open-first group.

A total of 5,259 (31%) patients underwent major amputation, 3,243 (30%) in the endovascular first group and 2,016 (34%) in the open first group. The median time to amputation for patients in the endovascular first group was 4.7 months (IQR 1.5 – 18.7) and 2.8 months (IQR 1.1 – 10.1) in the open first group. After propensity weighting, adjusted open first treatment was associated with worse AFS compared to endovascular first treatment (HR 1.16, 95% Confidence Interval (CI): 1.13–1.20, Figure 2).

Repeat interventions were performed in 6,136 (37%) patients, 4,112 (38%) were in the endovascular first group and 2,024 (34%) in the open first group. The median time to reintervention for patients in the endovascular first group was 4 months (IQR = 1.7 – 12.6) and 7.8 months (IQR = 3.1 – 19.1) in the open first group. Of the 4,112 patients in the endovascular group who had reintervention, 3,222 (78%) had a second endovascular procedure and 890 (22%) had an open procedure. In the open first group 1,176 (58%) had an endovascular procedure and the remaining 866 (42%) had a second open procedure. After propensity weighting, adjusted endovascular first treatment was associated with higher rates of reinterventions (HR: 1.19, 95% CI: 1.14–1.23, Figure 3).

Overall mortality for the study was 28% (n= 4,725). In the open first cohort, 1,588 (27%) patients died compared to 3,137 (29%) in the endovascular first cohort. The median time to death for patients treated with open surgery first compared to endovascular first was 16 months (IQR = 6–36.9) and 22 months (IQR = 8.5– 42.3) respectively. After propensity weighting there was no difference in adjusted overall mortality associated with open first treatment compared to endovascular first treatment (HR: 0.94, 95% CI: 0.89–1.11, Figure 4).

Discussion:

Patients with CLI have multiple comorbidities and choosing the initial treatment requires a customized therapeutic approach that balances patient factors with technical and anatomic limitations. Our work with this all-payer state-based data has shown that an initial open surgical bypass approach for patients with CLI was associated with worse AFS but decreased secondary procedures with no difference in overall mortality compared to an endovascular first approach.

The minimally invasive nature of endovascular therapy permits it to be applied to a wider patient population, specifically those with more comorbidities. We found in our study that patients who were treated with an endovascular first strategy were associated with more comorbid conditions. Additionally, many studies have shown an expansion of minimally invasive endovascular techniques to older patients in multiple areas of vascular surgery.[14] In a population based study of CLI treatment, Klaphake et al. found that when patients were offered an invasive treatment for limb salvage, older patients with increased comorbidities were more likely to be offered endovascular therapy instead of open surgical bypass.[15] Although our data demonstrates the endovascular group to be slightly younger, the difference is not clinically significant and the two groups can be considered to be of a similar age. This finding may be related to the increased number of comorbidities and population shift that is occurring in the United States due to the diabetes and obesity epidemic. Our own prior population based work showed patients with combined PAD and DM are younger and have a significantly higher risk of amputation than patients with PAD alone.[16] Unfortunately, we also showed an alarming increase in the number of amputations in these patients over time.[2] In 2016 the SAGE group released new statistics estimating that over the next 15 years the number of patients with CLI will double and this will be highest in the age groups of 45 to 64 and 65 to 70.[17]

Patients treated by open surgery first were 21% more likely to require amputation or die over the course of the entire study period compared to patients treated by an endovascular first approach despite their higher burden of chronic disease. The difference in AFS was driven by the higher amputation rates for patients who were treated with open surgery first. These findings may indicate that the severity of disease drove the selection of open surgery first and why we found a worse AFS in the open surgery group. The only level one trial to compare an open vs. endovascular first strategy, found no difference in AFS between an open or endovascular first treatment strategy until after two years at which time an open surgery first approach resulted in a 15% decrease in the risk of amputation or death.[5] While 75% of patients in the trial were treated for gangrene or tissue loss, there was no standardized classification of the degree tissue loss. In today's endovascular-first climate, the choice of open surgery first is likely due to more severe wounds in a patient with superior autologous conduit. However, data from the PREVENT III registry showed that 28% of patients do not have single segment great saphenous vein of adequate size.[18] Unfortunately, severity of wounds cannot be deduced by ICD-9-CM coding in an administrative data set and we can only hypothesize to the difference seen in this study.

While open surgery was associated with a decreased risk of reintervention, there was still 34% of patients in the open surgery first and 38% of patients in the endovascular first group who required reintervention. Primary patency at one year for endovascular treatment for infra-inguinal disease ranges from as low as 48% for balloon angioplasty, 66% for angioplasty plus stent placement, and as high as 89% for drug coated balloon angioplasty.[19, 20] In this study we are unable to separate the varied technologies due to the limitations of ICD-9-CM codes. We do anticipate that with the new ICD-10-CM data, we will be able to look at specific types of treatments. Primary patency for surgical bypass is not much better. The PREVENT III trial found that the primary patency at one year was only 68% when the best choice conduit, a single segment great saphenous vein > 3.5 mm in size, was used. Furthermore, when the distal target was a tibial artery, the patency was as low as approximately 58%.[18] While we continue to strive for improvements in endovascular technologies, we have made not made much progress in the last 20 years with the development of new surgical conduits or adjuncts to improve bypass patency. As a vascular community, more work needs to focus on improved patency of surgical bypasses as well. This is especially important as there are many patients who are not candidates for endovascular therapy due to anatomic limitations as well as many patients who do not have good single segment venous conduits.

This work has several limitations. First, our cohort was drawn from an administrative database, and all of the data rely on proper ICD-9-CM coding. Although we were able to create a distinct CLI cohort using the ICD-9-CM coding schema, errors in coding may allow inappropriate patients to be captured. Additionally, although we performed a look back to examine for prior revascularization procedures in the past five years, it is impossible to evaluate patients that may have been treated outside of California and then moved into the state. Another limitation is that the study represents the population of California and may limit its generalizability to other populations. Although California's population is diverse, it is similar in age and gender composition to that of the entire United States. The state does have a higher percentage of Hispanic and Asian populations than the rest of the country, allowing our data to provide more insight regarding Hispanic and Asian Americans than studies based on national Medicare data. Additionally, the use of an administrative database precludes certain patient-level variables that are clinically relevant such as disease severity, patient anatomy, lesion characteristics, presence of an adequate conduit, and wound healing. Furthermore, the dataset does not allow for the differentiation of the specific type of open or endovascular treatment such as the level of bypass and conduit used or plain balloon angioplasty versus drug coated balloon angioplasty. Finally, we were only able to capture patients who required inpatient hospitalization or had an outpatient procedure in a designated outpatient center as defined by the OSHPD database. Patients treated in an office-based outpatient center were not captured and the outcomes for patients who undergo endovascular treatment in these facilities are not considered.

Considering these limitations, this study gives an idea of generalized real-world outcomes across hospitals with varying capabilities when open therapy first is compared to an endovascular first approach. In conclusion, within the current practice environment, patients with CLI have multiple comorbidities and initial surgical bypass appears to be associated with poorer AFS compared to an endovascular first approach with no difference in overall mortality. It is difficult to conclude the reason behind this finding using the present dataset; however, we hypothesize that this may be in part due to the increased severity of ischemic wounds at the time of presentation. The direction of future studies will focus on controlling for severity to further evaluate the outcome of these two therapeutic strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is Known:

- Limited level 1 data with only one randomized controlled trial that demonstrated there was no difference in amputation free survival between an endovascular or open surgery first strategy for out to two years.
- It is currently unclear whether open first therapy or endovascular first results in better amputation free survival in patients with critical limb ischemia.

What the Study Adds:

- Gives a pragmatic overview of the amputation free survival of patients who were treated with an endovascular first strategy throughout hospitals in a state with a highly diverse ethnic population.
- Suggests that endovascular first may be at least equivalent to open therapy first in terms of amputation free survival.

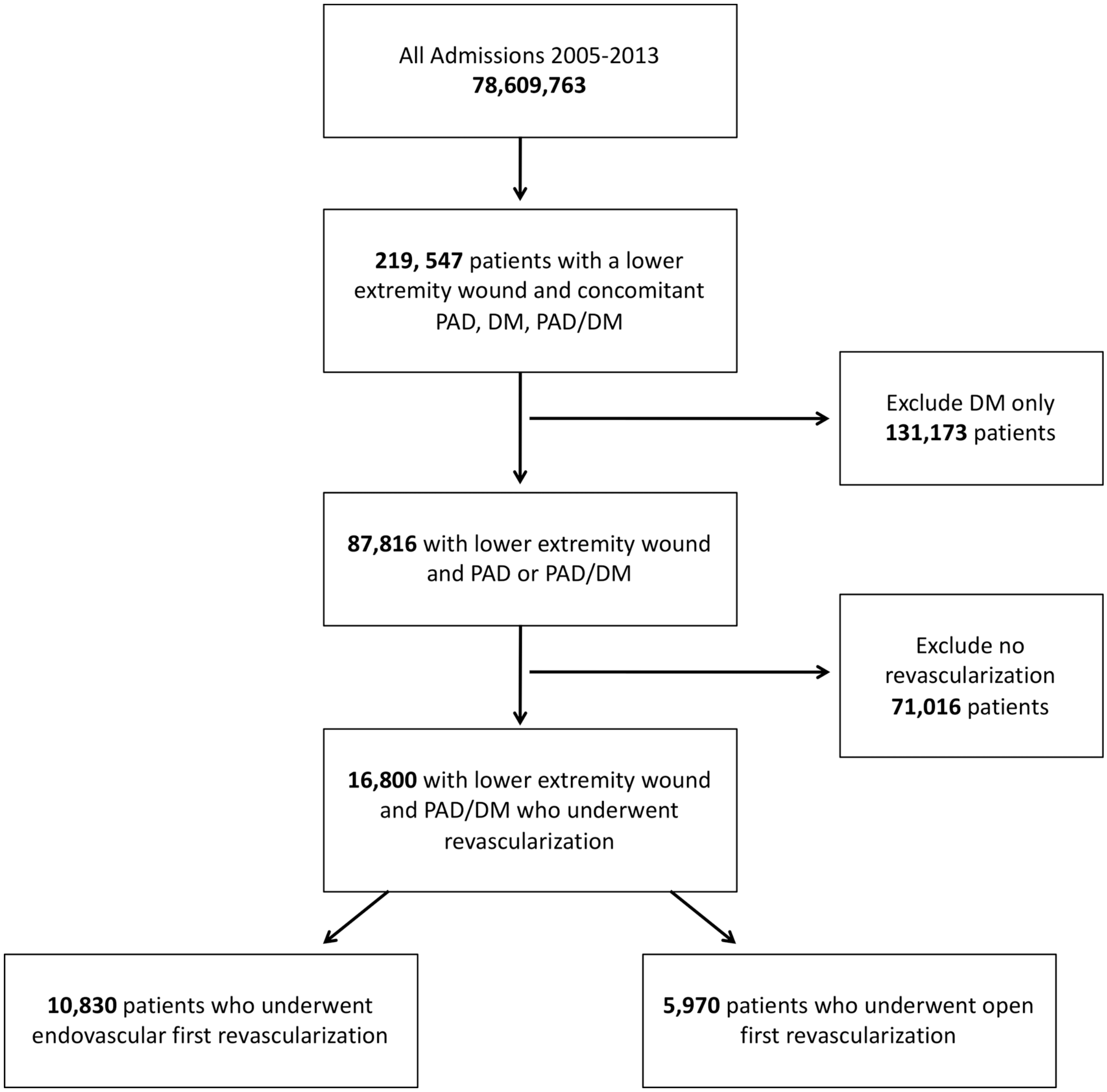


Figure 1. Patient Cohort Development

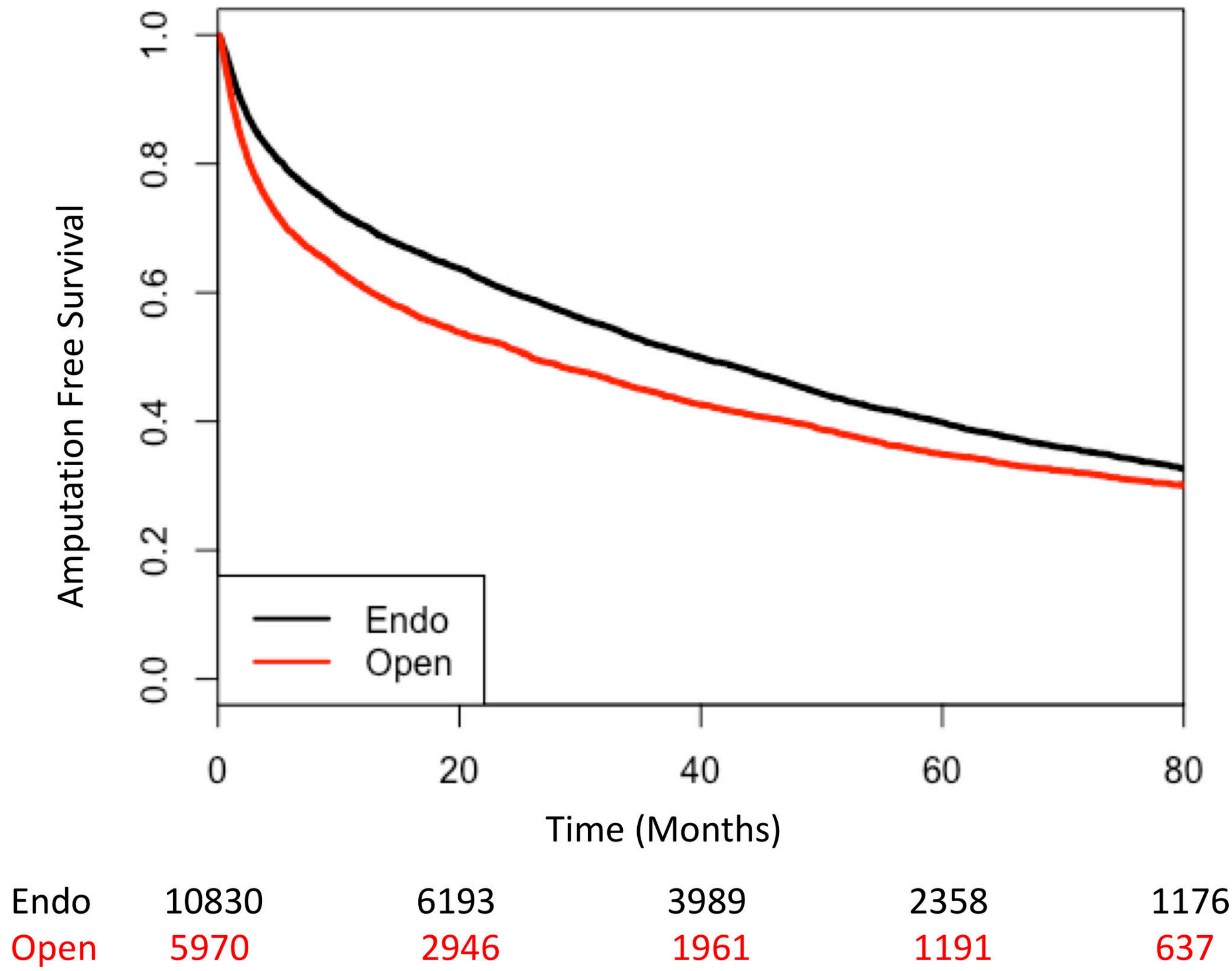
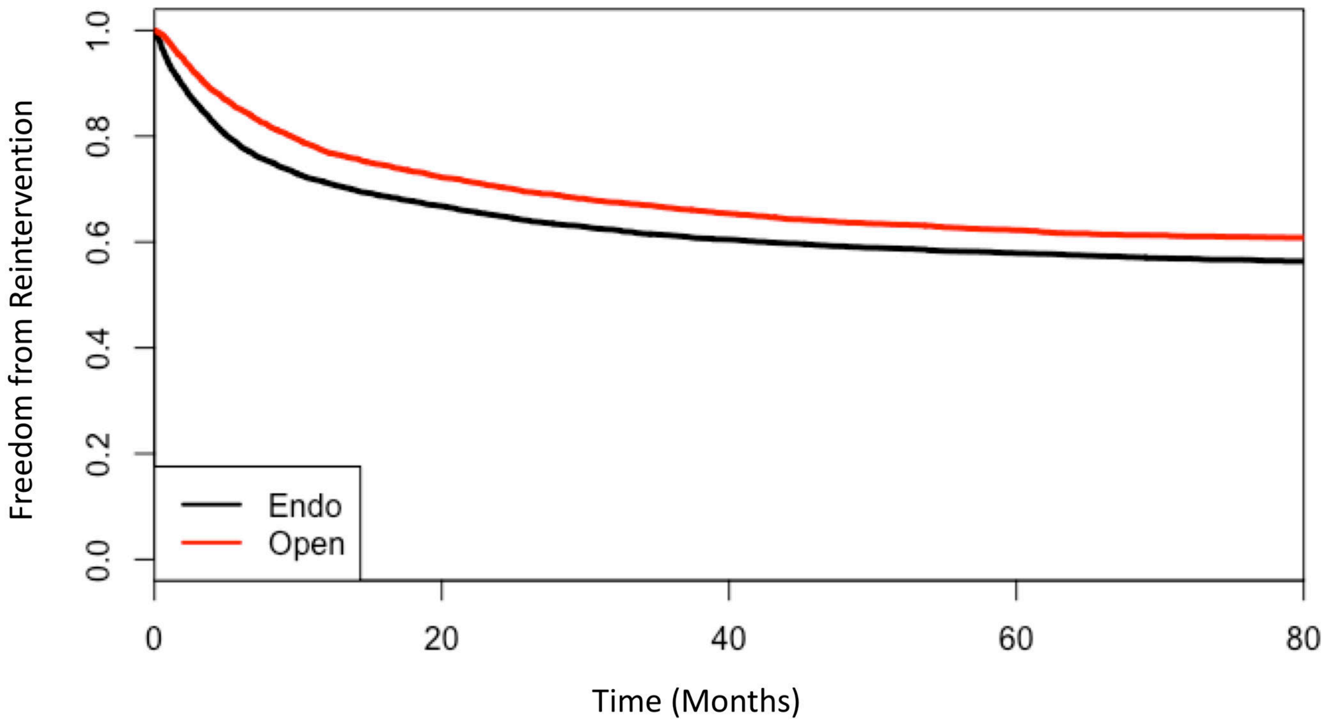


Figure 2. Kaplan-Meier curve showing amputation free survival after open or endovascular first treatment.

After adjusting for “patient ability” and hospital revascularization experience and after propensity score weighting, open first treatment was associated with worse AFS than endovascular first treatment (HR of 1.16, 95% CI: 1.13–1.20, for risk of major amputation or death).



Endo	10830	4024	2212	1232	633
Open	5970	2106	1233	698	366

Figure 3. Kaplan-Meier curve showing need for repeat interventions after open or endovascular first treatment.

After adjusting for “patient ability” and hospital revascularization experience and after propensity score weighting, endovascular first treatment was associated with more reinterventions compared to open first treatment (HR 1.19, 95% CI: 1.14–1.23).

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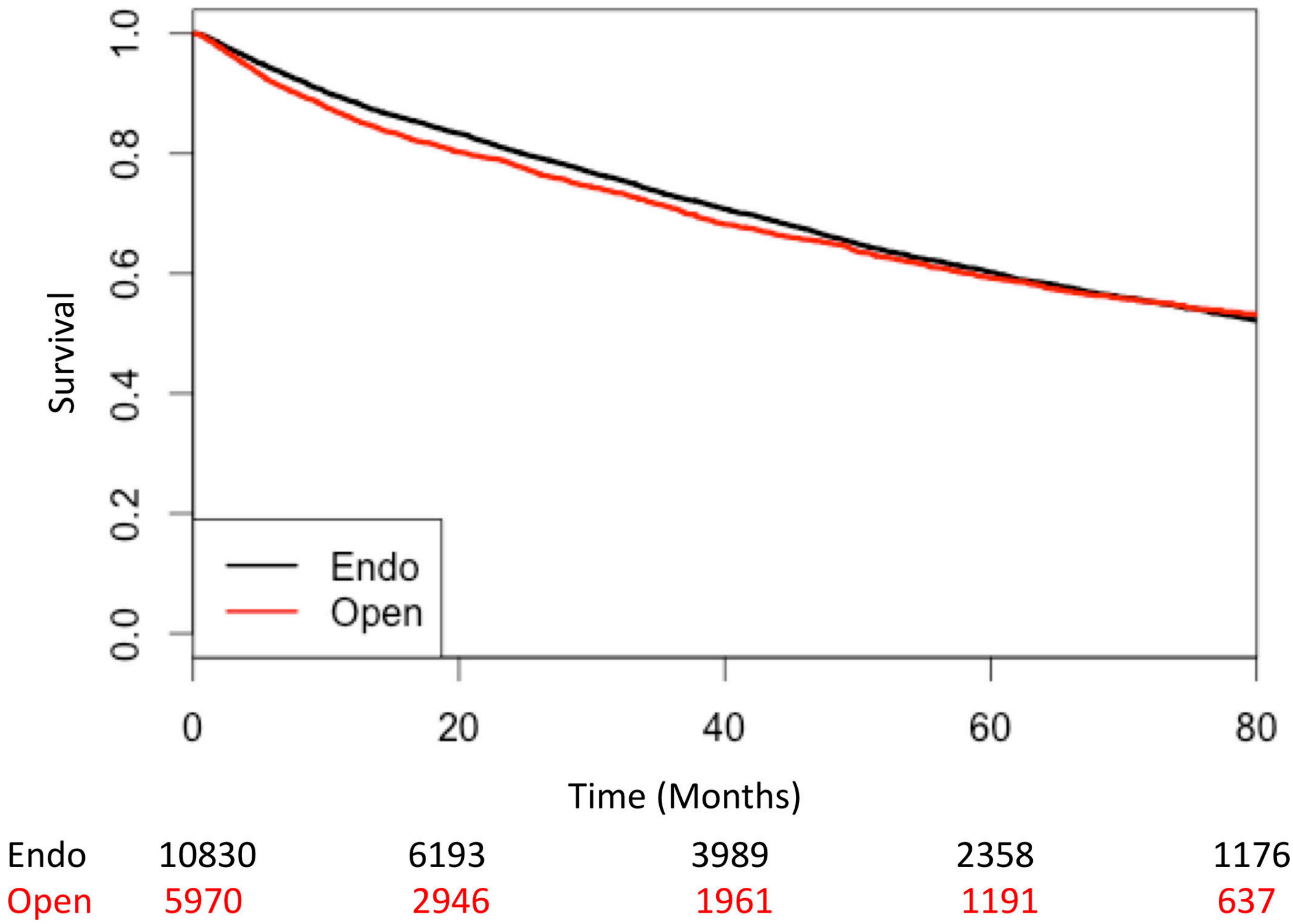

Figure 4. Kaplan-Meier curve showing overall mortality for open vs endovascular first therapy.
After adjusting for "patient ability" and hospital revascularization experience and after propensity score weighting, no difference in overall mortality was seen between open first and endovascular first treatment (HR 0.94, 95% CI: 0.89–1.11).

Table 1.

Patient characteristics of the entire cohort before propensity score weighting.

Continuous variables were compared using the Wilcoxon rank sum test and categorical values using χ^2 or Fisher exact tests. P<0.05 is considered statistically significant.

Variable	All n (%)	Open surgery first n (%)	Endovascular first n (%)	P-value
Total	16800	5970 (36)	10830 (64)	
Male	9886 (59)	3542 (59)	6344 (59)	0.35
Age (mean ± SD)	71±12	71±12	70±12	<0.001
Smoker	2511 (15)	1206 (20)	1305 (12)	<0.001
Payer Category				
-Medicare	11259 (67)	3923 (66)	7336 (68)	0.007
-Private Coverage	3424 (20)	1354 (22)	2070 (19)	<0.001
-Medi-Cal	1477 (9)	481 (8)	996 (9)	0.01
-Self Pay	309 (2)	104 (2)	205 (2)	0.52
-County Indigent Program	86 (0.5)	19 (0.5)	67 (0.6)	0.01
-Other Government	245 (1.5)	89 (1.5)	156 (1.4)	0.85
Race				
-White	8097 (48)	3168 (53)	4929 (46)	<0.001
-Hispanic	4150 (25)	1216 (20)	2934 (27)	<0.001
-African American	1623 (10)	635 (11)	988 (9)	0.002
-Asian	849 (6)	277 (5)	572 (5)	0.07
-Other / Unknown	2081 (11)	674 (11)	1407 (13)	0.001
Coronary Artery Disease	5518 (33)	1882 (32)	3636 (34)	0.007
Congestive Heart Failure	3000 (18)	921 (15)	2079 (19)	<0.001
Renal Failure	5396 (32)	1461 (24)	3935 (36)	<0.001
Diabetes Mellitus	7562 (70)	3439 (58)	7562 (65)	<0.001