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Publication Date

2024-03-01

DOI

10.1016/j.jvs.2024.02.033

Peer reviewed

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PII: S0741-5214(24)00410-5

DOI: https://doi.org/10.1016/j.jvs.2024.02.033

Reference: YMVA 13512

To appear in: *Journal of Vascular Surgery*

Received Date: 5 August 2023

Revised Date: 28 January 2024

Accepted Date: 7 February 2024

Please cite this article as: Patel RJ, Zarrintan S, Vootukuru NR, Allah SH, Gaffey A, Malas MB, Long-Term Outcomes in the Smoking Claudicant after Peripheral Vascular Interventions, *Journal of Vascular Surgery* (2024), doi: https://doi.org/10.1016/j.jvs.2024.02.033.

Long-Term Outcomes in the Smoking Claudicant after Peripheral Vascular Interventions

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Presented at 2023 Vascular & Endovascular Surgery Annual Spring Meeting, National Harbor, MD, June 14-17, 2023

Disclosures:

None

Funding:

Rohini J. Patel is funded through the National Library of Medicine, T15 Postdoctoral Training Grant Fellowship Program in Biomedical Informatics (Grant T15LM011271)

Running Title:

PVI in Smoking Claudicants

Keywords:

Smoking, Peripheral Vascular Intervention, Amputation, Claudicant

ARTICLE HIGHLIGHTS

Type of Research: A retrospective review of prospectively collected Vascular Quality Initiative (VQI) VISION data

Key Findings: Propensity matching of 3,160 pairs of never and former smokers found no difference in survival, reintervention or amputation free survival. However, 3,750 pairs of current and former smokers found a significant increase in survival [HR = 1.18, p =0.01] and amputation free survival [HR = 1.16, p=0.01] in former smokers.

Take Home Message: Former smokers have better overall survival and amputation free survival when compared to current smokers, while former smokers mimic nonsmokers at 5-year outcomes for survival, freedom from reintervention and amputation free survival.

TABLE OF CONTENTS SUMMARY

This is a propensity score matched study with 3,160 pairs of never/former smokers and 3,750 pairs of current/former smokers. Former smokers have better survival and amputation free survival compared to

current smokers, while former smokers mimic nonsmokers at 5 years for survival, reintervention and amputation free survival.

ABSTRACT

Objectives

Emphasis on tobacco cessation given the urgent and emergent nature of vascular surgery is less prevalent than standard elective cases such as hernia repairs, cosmetic surgery, and bariatric procedures. The goal of this study is to determine the effect of active smoking on claudicating individuals undergoing peripheral vascular interventions (PVI). Our goal is to determine if a greater emphasis on education should be placed on smoking cessation in non-urgent cases scheduled through clinic visits and not the Emergency Department.

Methods

This study was performed using the multi-institution de-identified Vascular Quality Initiative-Medicare-Linked database (VISION). Claudicants who underwent PVI for peripheral arterial occlusive disease between 2004-2019 were included in our study. Our final sample consisted of a total of 18,726 patients: 3,617 (19.3%) nonsmokers (NS), 9,975 (53.3%) former smokers (FS) and 5,134 (27.4%) current smokers (CS). We performed propensity score matching (PSM) on 29 variables [age, gender, race, ethnicity, treatment setting (outpatient or inpatient), obesity, insurance, hypertension, diabetes, CAD, CHF, COPD, CKD, previous CABG, CEA, major amputation, inflow treatment, prior bypass or PVI, preop medications, level of treatment, concomitant endarterectomy, and treatment type (atherectomy, angioplasty, stent)] between NS versus FS and FS versus CS. Outcomes were long-term (five-year) overall survival (OS), limb salvage (LS), freedom from reintervention (FR) and amputation free survival (AFS).

Results

PSM resulted with 3,160 well matched pairs of NS and FS and 3,750 well matched pairs of FS and CS. There was no difference between FS and NS in terms of OS [HR = 0.94, 95% CI 0.82-1.09, p=0.43], FR [HR = 0.96, 95% CI 0.89-1.04, p=0.35], or AFS [HR = 0.90, 95% CI 0.79-1.03, p=0.12]. However, when compared to CS, we found FS to have a higher OS [HR = 1.18, 95% CI 1.04-1.33, p =0.01], less FR [HR = 0.89, 95% CI 0.83-0.96, p=0.003] and greater AFS [HR = 1.16, 95% CI 1.03-1.31, p=0.01].

Conclusion

This multi-institutional Medicare-linked study looking at elective PVI cases in PAD patients presenting with claudication found that former smokers have similar 5-year outcomes in comparison to non-smokers in terms of OS, FTR and AFS. Additionally, current smokers have lower overall survival and amputation free survival when compared to former-smokers. Overall, this suggests that smoking claudicants should be highly encouraged and referred to structured smoking cessation programs or even required to stop smoking prior to elective PVI due to the perceived 5-year benefit.

INTRODUCTION

Peripheral arterial disease (PAD) continues to be a prominent cardiovascular concern with chronic limb ischemia representing long-term fears of mortality, amputation and decreased quality of life.(1,2) The prevalence of PAD in adults in the United States over the age of 60 is 12.2% and cigarette smoking is considered a major risk factor in this development.(3–5) Within the spectrum of PAD, claudication is associated with functional limitations and reduced quality of life.(6,7) Previous studies have found that smoking is linked to many vascular disease processes and that smoking cessation can help reverse some of the deleterious effects of smoking on a patient's vessels, such as decreased intimal hyperplasia and improved compliance.(3,5,8) Smoking is known to increase complications, including poor wound healing, coagulation abnormalities, and cardiac and pulmonary ramifications.(9) A Vascular Quality Initiative study of lower extremity bypass and open abdominal aortic aneurysm cases found that smoking within 8 weeks of surgery was associated with increased pulmonary complications.(10) Additionally, a propensity score matched analysis of claudicants undergoing lower extremity bypass in the Vascular Quality Initiative found that former smokers have better overall and amputation free survival compared to current smokers at five years and that former and never smokers have no difference in survival or reintervention.(11)

A randomized trial with 156 patients found that a physician recommendation of smoking cessation and nicotine replacement therapy were associated with an increased odd of smoking cessation.(12) A Cochrane review in 2006 demonstrated that postoperative complications including death, pulmonary issues, wound infections and length of stay all could be negatively influenced by a recent history of smoking.(13) Additionally, general and plastic surgery has found associations with active smoking and wound complications in a meta-analysis leading to the

recommendation of smoking cessation prior to elective repair of multiple procedures.(14) In Vascular Surgery practice, smoking cessation prior to endovascular peripheral vascular interventions within the claudicant population remains inconsistent.

Emphasis on tobacco cessation given the urgent and emergent nature of vascular surgery is less prevalent than standard elective case such as hernia repairs, cosmetic surgery, and bariatric procedures. Across specialties, elective surgical procedures are commonly denied to active smokers. Given the base population of active smokers with vascular disease, smoking cessation is encouraged but is not required the way it is in General Surgery.(15) Overall, smoking cessation is associated with decreased morbidity and mortality in patients with PAD and represents a level 1A recommendation by the Society of Vascular Surgery.(16) The goal of this study is to determine the effect of active smoking on individuals undergoing endovascular peripheral vascular interventions (PVI) for claudication. Our goal is to determine if a greater emphasis on education should be placed on smoking cessation in non-urgent cases scheduled through clinic visits and not the Emergency Department.

METHODS

Dataset

The Vascular Quality Initiative (VQI) is a prospectively collected registry. The registry contains preoperative, intraoperative and postoperative variables at approximately 1,000 centers in the United States and Canada.(17,18) Additionally, the Vascular Implant Surveillance and Interventional Outcomes Network (VISION) is a partnership between VQI and MDEpiNet which links VQI data to Medicare data allowing long-term outcomes analysis.(19) This particular study was conducted using the peripheral vascular intervention dataset after obtaining approval from the

VQI Research Advisory Committee for VQI-VISION data (Protocol #4991). The VQI-VISION is a de-identified registry and therefore individual consent and Institutional Review Board approval were not required.

Population

A retrospective analysis was performed on all patients who had an infra-inguinal peripheral vascular intervention (PVI) between 2004-2019. Inclusion criteria was any patient over the age of 18, with arterial occlusive disease pathology, and claudication symptoms. Exclusion criteria was any concomitant suprainguinal procedures, aneurysm pathology, or acute limb ischemia symptoms. Additionally, patients with missing data regarding smoking status were excluded. Within this cohort, smoking status was used to create three subgroups of never smokers (NS), former smokers (FS) defined as quitting over one month prior to PVI, and current smokers (CS) defined as smoking cigarettes, pipes, or cigars within the past month.

Variables

Baseline characteristics including demographics [age, sex, race, ethnicity, obesity, insurance type], comorbidities [diabetes, hypertension, congestive heart failure (CHF), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD)], surgical history [prior carotid endarterectomy, carotid artery stent, coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI), prior major amputation, prior inflow procedure, prior lower extremity intervention], preoperative and discharge medications [aspirin, P2Y12 inhibitors, statins, anticoagulation], and procedure details [inpatient versus outpatient setting, treatment with angioplasty/stent/atherectomy, concomitant endarterectomy, level of treatment (supragenicular versus infragenicular)] were collected.

Outcomes

Long-term outcomes were assessed at five years. Primary outcomes included freedom from reintervention (FR) and amputation free survival (AFS). Secondary outcomes included overall survival (OS) and limb salvage (LS). Amputation was defined as any amputation above the transmetatarsal in the index limb. Reintervention was defined as any intervention following the index procedure.

Statistical Analysis

Continuous and binary variables were analyzed using Student's t-test, rank-sum test and Pearson's chi-squared test, respectively. Given the significant variation in baseline characteristics between NS, FS, and CS we elected to use propensity score matching (PSM) based on smoking status. One-to-one PSM without replacement was used to balance the cohorts on 29 dimensions listed in Table I by the nearest neighbor principle with a caliper size of 0.1 for FS and CS and a caliper of 0.01 for NS and FS. An adequate match was achieved with an absolute standardized difference <0.10 in all baseline covariates. Kaplan-Meier survival estimates, log-rank test and univariate Cox regression models were used to analyze outcomes of interest. All analyses were performed using Stata 17.0 (StataCorp, College Station, Texas).

RESULTS

There were a total of 18,726 patients who underwent PVI between 2004-2019 and met inclusion criteria prior to matching. Of these patients, 9,975 (53.3%) self-categorized as former smokers (FS), 5,134 (27.4%) self-identified as current smokers (CS) and 3,617 (19.3%) were never smokers (NS).

Baseline Characteristics - Former versus Current Smokers

When comparing FS and CS, 9,975 (66.0%) were FS and 5,134 (34.0%) were CS. Prior to matching, CS were younger (67.5 ± 8.3 years versus 73.2 ± 7.9 years, std diff=0.706) and had a higher proportion of COPD (37.4% versus 26.6%, std diff=0.233) while FS had a greater proportion of patients with hypertension (92.6% versus 87.9%, std diff=0.157), diabetes (47.3% versus 40.6%, std diff=0.136), CAD (53.7% versus 43.6%, std diff=0.204) and CKD (45.2% versus 31.3%, std diff=0.289). Of note, there was no significant difference in level of treatment (FS had 76.7% suprageniculate and 23.3% infrageniculate while CS had 80.4% suprageniculate and 19.6% infrageniculate, std diff=0.091) or in type of treatment (FS had 33.7% angioplasty, 36.6% stent, 20.2% atherectomy, 9.5% stent and angioplasty while CS had 30.7% angioplasty, 40.1% stent, 19.7% atherectomy, and 9.5% stent and angioplasty, std diff=0.077). After matching we were left with 3,750 pairs of FS and CS who had a PVI [Table I] with a standardized difference <0.10. This cohort was well balanced and matched on 29 variables (for example, age, preoperative statin use, level of treatment [suprageniculate or infrageniculate], preoperative anticoagulation use, type of treatment [angioplasty, stent, atherectomy, or combination], obesity, concomitant endarterectomy, hypertension, diabetes, preoperative aspirin use, CHF, COPD, CKD, CABG/PCI, prior lower extremity intervention [bypass or PVI] and prior major amputation) to a caliper of 0.10.

Baseline Characteristics - Never versus Former Smokers

We then compared NS 3,617 (26.6%) to FS were 9,975 (73.4%). Prior to matching, there were significant differences in level of treatment (NS had 63.4.% suprageniculate and 36.6% infrageniculate while FS had 76.7% suprageniculate and 23.3% infrageniculate, std diff=0.294) and in type of treatment (NS had 36.9% angioplasty, 33.6% stent, 22.0% atherectomy, 7.5% stent and angioplasty while FS had 33.7% angioplasty, 36.6% stent, 20.2% atherectomy, and 9.5% stent

and angioplasty, std diff=0.111). After matching we were left with 3,160 pairs of NS and FS who had a PVI [Table II] with a standardized difference <0.10. This cohort was well balanced and matched on 29 variables (for example, age, gender, race, ethnicity, concomitant endarterectomy, level of treatment [suprageniculate or infrageniculate], discharge statin use, preoperative aspirin use, diabetes, prior inflow treatment, discharge anticoagulation use, COPD, CKD, prior lower extremity intervention [bypass or PVI], prior CEA or CAS, prior major amputation and type of treatment [angioplasty, stent, atherectomy, or combination]) to a caliper of 0.01.

Outcomes – Former versus Current Smokers

Table III is the five-year outcomes for OS, FR, LS and AFS. Prior to matching when comparing FS to CS there was a significantly greater OS (67.1% versus 65.5%, p=0.005) and FR (49.6% versus 48.0%, p=0.035) in CS compared to FS and no significant difference in LS or AFS. However, after matching we found FS had a significantly greater OS (70.9% versus 64.4%, p=0.002) and AFS (68.0% versus 62.0%, p=0.003) compared to CS. There was no significant difference in LS and FR was significantly higher in CS (50.7% versus 47.7%, p=0.003).

Table IV represents the Cox-regression five-year analysis. Prior to matching, there was no significant difference in FR, LS or AFS (HR=0.94, 95%CI = 0.86-1.01, p=0.109) [Figure 1A] in CS compared to FS. Current smokers were found to have a 10% decrease in mortality compared to former smokers (HR=0.90, 95%CI = 0.83-0.98, p=0.016). However, once matching was performed, CS were found to have an 18% increased risk of mortality (HR=1.18, 95%CI = 1.04-1.33, p=0.010), 14% increased risk of major amputation (HR=1.14, 95%CI = 0.87-1.51, p=0.346), and 16% increased risk of major amputation or death (HR=1.16, 95%CI = 1.03-1.31, p=0.013) [Figure 1B].

Outcomes – Never versus Former Smokers

Table III is the five-year outcomes for OS, FR, LS and AFS. Prior to matching when comparing NS to FS there was a significantly greater OS (65.5% versus 62.0%, p<0.001), LS (94.4% versus 91.6%, p<0.001) and AFS (63.1% versus 58.7%, p<0.001) in FS compared to NS and no significant difference in FR. After matching we found FS had a significantly greater LS (94.4% versus 91.7%, p<0.001) and AFS (60.9% versus 59.5%, p=0.030) compared to NS. There were no significant differences in OS and FR in FS compared to NS.

Table IV represents the Cox-regression five-year analysis. Prior to matching, former smokers had a significantly decreased risk of all-cause mortality (HR=0.85, 95%CI = 0.77-0.95, p=0.003), major amputation (HR=0.80, 95%CI = 0.47-0.70) and a 20% decreased risk of major amputation or death (HR=0.80, 95%CI = 0.73-0.89) [Figure 2A] compared to NS. However, after matching there was no significant difference between NS and FS in terms of all-cause mortality, reintervention, or major amputation or death (HR=0.90, 95%CI = 0.79-1.03), p=0.115) [Figure 2B].

DISCUSSION

This study evaluated the outcomes in currents smokers, former smokers and never smokers after a peripheral vascular intervention. After 5 years, former smokers and never smokers were found to have no difference in overall survival, freedom from reintervention, or amputation free survival. However, when compared to current smokers, former smokers were found to have improved overall survival and amputation free survival. These results demonstrate the value of smoking cessation prior to peripheral intervention for patients with claudication.

PVI is the mainstay of treatment for patients with symptomatic PAD.(20) The majority of these interventions are performed electively, in a non-urgent setting allowing the capacity for smoking cessation to take place prior to these procedures. This has even led to the idea that maybe

surgeons should not be performing an operation if medical management including smoking cessation is not completely optimized in patients with non-limb threating PAD.(21)

Smoking is a major contributor for development and progression of PAD due to the exacerbation of oxidative stress and detrimental effects on endothelial function, lipoprotein metabolism, and coagulation.(22) These effects may be reversible as seen in studies that show smoking cessation for those with PAD has improved overall survival and amputation free survival.(11,23,24) Additionally, reduced post-procedural complications including wound infections, respiratory complications, thrombosis, graft failure, kidney damage, sepsis, and neurological function were observed in nonsmokers compared to smokers in a large observational cohort study of propensity score matching patients in the Veterans Affairs Surgical Quality Improvement Program of 14,350 revascularization cases.(25)

These studies suggest that smoking cessation may be a valuable addition to treatment, given the dual benefit of slowing the progression of PAD overall, as well as improving the outcomes following endovascular intervention. Smoking cessation prior to surgery may be a particularly effective time to educate patients. This benefit was seen in a study of 14,000 patients under the Vascular Physician Offer and Report (VAPOR) trial where target education with physician-delivered advice, telephone counseling and nicotine replacement therapy was conducted.(26) In this trial, 35% of patients who received at least one component had stopped smoking within 30 days.(26)

Additionally, in the Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories (PORTRAIT) registry, 1300 patients were followed for up to one year and found that patients were more likely to quit smoking early in their treatment course, however, continued cessation support is crucial to prevent relapse.(27)

Furthermore, as the typical definition of smoking has evolved over time from cigars and cigarettes to tobacco and now to smokeless tobacco products, the effect on PAD is less understood. The Atherosclerosis Risk in Communities study found that for individuals who use smokeless tobacco, the incidence of PAD is similar to those who smoke cigarettes, therefore suggesting that smokeless tobacco is not necessarily a safe alternative.(28)

The goal of this manuscript is to demonstrate that in vascular patients undergoing PVI procedures, there are striking differences in the 5-year long-term outcomes between individuals based on smoking status. Overall, we found that current smokers fare worse that former smokers, however, former smokers attain similar outcomes to individuals who never smoked. While our manuscript is meant to encourage individuals to stop smoking and place a greater emphasis on smoking cessation education and strategies on our profession, our overall recommendation for the treatment of claudication in smokers is as follows. Given the low acuity of claudication compared to acute limb ischemia we recommend not offering elective PVI procedures to smokers. Claudication represents a unique vascular pathology that is not immediately life threatening and therefore procedures do not have to be performed while individuals are still smoking.

There is a lack of literature overall comparing smoking status in patients with PVI using the VQI. This study represents the only propensity score matched VQI study comparing never smokers to former smokers and former smokers to current smokers with claudication who underwent PVI. A similar large volume study using the Veterans Affairs data focused on the impact on organ systems but did not specifically address amputation free survival or reintervention.(25) Overall, our study demonstrates that smoking cessation should be encouraged during the preoperative period and that patients who quit smoking can have outcomes following PVI similar to patients who never smoked. A greater emphasis on smoking cessation education

should be placed on patients undergoing elective vascular surgery cases for PVI and formal smoking cessation counseling and pharmacological therapies may be of greatest benefit.

Limitations

This is a retrospective study and inherently we cannot determine the causal association between PVI outcomes and smoking status. Additionally, this study was performed using the VQI VISION database which is based on Medicare claim data and therefore does not account for younger patients and patients not on Medicare. The VISION database can be subject to data availability, as are all large registries, can have under-reporting since all outcomes are self-reported, although less likely due to third party audits, and VISION does not code laterality for reinterventions. In terms of smoking status, granular details regarding duration of smoking or change during follow-up is not captured. Smoking recidivism rates are not provided in the cohort. Overall, for any patient who stops smoking prior to intervention and then starts smoking again once their intervention in complete will not be accurately captured in this dataset. Future studies that prospectively follow patients should focus on change in smoking status pre-procedure, intra-procedure, and in a defined follow-up window. Additionally, amputation is defined as any level above transmetatarsal in the index limb and therefore does not follow the standard major amputation definition. Finally, we do not have information regarding cause of death and this could be attributed to cardiac issues, malignancy or limb ischemia. Overall, we used propensity score matching to attempt to mitigate confounding factors as much as possible.

CONCLUSION

This is the largest study of its kind and emphasizes a multicenter national Medicare-linked analysis demonstrating the effects of smoking on patients with claudication undergoing peripheral

vascular interventions. Current smokers had increased all-cause mortality and worse amputation free survival compared to former smokers. Furthermore, former smokers were found to have no difference in overall mortality, reintervention or amputation free survival compared to individuals who never smoked. This demonstrates that 5-year outcomes of individuals who quit smoking is similar to those who never smoked. This study demonstrates the importance of smoking cessation discussions with claudicants before and after PVI. Further studies are needed to validate our findings.

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Table I: Baseline Characteristics of Former Smokers and Current Smokers Before and After Matching

Variable	Before Matching N=15,109			After Matching N=7,500		
	Former Smokers (FS) N=9,975 (66.0%)	**Current Smokers (CS) N=5,134 (34.0%)**	**Standardized Difference**	**Former Smokers (FS) N=3,750 (50.0%)**	**Current Smokers (CS) N=3,750 (50.0%)**	**Standardized Difference**
Age	73.2 ± 7.9	67.5 ± 8.3	0.70644	69.2 ± 7.6	69.5 ± 7.0	-0.04163
Gender			0.03420			0.00165
Male	6405 (64.2)	3212 (62.6)		2329 (62.1)	2332 (62.2)	
Female	3570 (35.8)	1922 (37.4)		1421 (37.9)	1418 (37.8)	
Race			0.11191			0.01023
White	8481 (85.0)	4149 (80.8)		3071 (81.9)	3057 (81.5)	
Non-white	1491 (15.0)	983 (19.2)		677 (18.1)	692 (18.5)	
Ethnicity			0.00650			0.02504
Non-Hispanic	9652 (97.0)	4959 (96.9)		3610 (96.4)	3623 (96.9)	
Hispanic	298 (3.0)	159 (3.1)		134 (3.6)	117 (3.1)	
PVI Setting			0.17520			0.01900
Outpatient	3765 (72.7)	1842 (72.8)		1491 (72.3)	1526 (73.2)	

Inpatient	1415 (27.3)	687 (27.2)		570 (27.7)	559 (26.8)	
Obesity			0.17520			0.01352
Non-obese	6321 (63.5)	3667 (71.7)		2676 (71.4)	2653 (70.7)	
Obese	3632 (36.5)	1449 (28.3)		1074 (28.6)	1097 (29.3)	
Insurance Type			0.03463			0.02668
Medicare	8175 (89.7)	4151 (88.6)		3354 (89.7)	3324 (88.9)	
Non-Medicare	939 (10.3)	533 (11.4)		386 (10.3)	418 (11.1)	
Hypertension	9213 (92.6)	4506 (87.9)	0.15696	3360 (89.6)	3382 (90.2)	0.01946
Diabetes	4714 (47.3)	2079 (40.6)	0.13558	1536 (41.0)	1575 (42.0)	0.02111
Coronary Artery Disease	5355 (53.7)	2234 (43.6)	0.20423	1773 (47.3)	1765 (47.1)	0.00453
Congestive Heart Failure	1760 (17.7)	661 (12.9)	0.13292	520 (13.9)	525 (14.0)	0.00385
Chronic Obstructive Pulmonary Disease	2648 (26.6)	1917 (37.4)	0.23311	1291 (34.4)	1279 (34.1)	0.00674
Chronic Kidney Disease	4480 (45.2)	1596 (31.3)	0.28843	1262 (34.4)	1293 (34.4)	0.01744
Coronary Artery Bypass Graft/Percutan	4373 (48.0)	1687 (36.0)	0.24513	1478 (39.4)	1469 (39.2)	0.00491

eous Coronary Intervention						
History of Carotid Endarterectomy and Carotid Artery Stent	640 (6.5)	214 (4.2)	0.10103	167 (4.5)	168 (4.5)	0.00123
Prior Major Amputation	185 (1.9)	73 (1.4)	0.03376	55 (1.5)	59 (1.6)	0.00872
Prior Inflow Treatment	1795 (18.1)	892 (17.6)	0.01452	636 (17.0)	673 (18.0)	0.02625
Prior Lower Extremity Intervention	6259 (62.8)	3000 (58.5)	0.l08794	2208 (58.9)	2263 (60.3)	0.02989
Aspirin	7896 (79.2)	3868 (75.4)	0.09046	2877 (76.7)	2892 (77.1)	0.00949
P2Y12 Inhibitors	5189 (52.0)	2709 (52.8)	0.01514	1940 (51.7)	2065 (55.1)	0.06658
Statin	7869 (78.9)	3736 (72.8)	0.14313	2833 (75.5)	2862 (76.3)	0.01809
Anticoagulation	1611 (16.2)	591 (11.5)	0.13467	454 (12.1)	483 (12.9)	0.02339
Concomitant Endarterectomy	487 (4.9)	184 (3.6)	0.06495	130 (3.5)	144 (3.8)	0.01990
Level of Treatment			0.09056			0.02490
Above knee	7650 (76.7)	4128 (80.4)		2983 (79.5)	2945 (78.5)	

Below knee	2325 (23.3)	1006 (19.6)		767 (20.5)	805 (21.5)	
Type of Treatment			0.07740			0.07131
Plain Angioplasty	3292 (33.7)	1550 (30.7)		1253 (33.4)	1173 (31.3)	
Stent	3581 (36.6)	2023 (40.1)		1331 (35.5)	1459 (38.9)	
Atherectomy	1976 (20.2)	993 (19.7)		796 (21.2)	762 (20.3)	
Stent and Angioplasty	934 (9.5)	479 (9.5)		370 (9.9)	356 (9.5)	
Discharge Aspirin	8307 (83.6)	4208 (82.5)	0.02911	3090 (82.7)	3106 (83.3)	0.01734
Discharge P2Y12 Inhibitors	8141 (81.9)	3952 (77.4)	0.11121	2968 (79.4)	2986 (80.1)	0.01732
Discharge Statin	7773 (78.2)	4057 (79.5)	0.03171	2997 (80.2)	3020 (81.0)	0.02158
Discharge Anticoagulation	1818 (18.3)	728 (14.3)	0.10933	551 (14.7)	564 (15.1)	0.01090

Table II: Baseline Characteristics of Never Smokers and Former Smokers Before and After Matching

Variable	Before Matching N=13,592			After Matching N=6,320		
	Never Smokers (NS) N=3,617 (26.6%)	**Former Smokers (FS) N=9,975 (74.4%)**	**Standardized Difference**	**Never Smokers (NS) N=3,160 (50.0%)**	**Former Smokers (FS) N=3,160 (50.0%)**	**Standardized Difference**
Age	73.3 ± 9.5	73.2 ± 7.9	0.24579	74.9 ± 9.5	75.0 ± 8.3	-0.00477
Gender			0.50481			0.01983
Male	1438 (39.8)	6405 (64.2)		1365 (43.2)	1334 (42.2)	
Female	2179 (60.2)	3570 (35.8)		1795 (56.8)	1826 (57.8)	
Race			0.17613			0.06684
White	2829 (78.3)	8481 (85.0)		2518 (79.7)	2431 (76.9)	
Non-white	786 (21.7)	1491 (15.0)		642 (20.3)	729 (23.1)	
Ethnicity			0.18267			0.04196
Non-Hispanic	3361 (93.1)	9652 (97.0)		2992 (94.7)	2961 (93.7)	
Hispanic	251 (6.9)	298 (3.0)		168 (5.3)	199 (6.3)	
PVI Setting			0.09431			0.05802
Outpatient	1218 (68.4)	3765 (72.7)		1078 (69.2)	1163 (71.9)	

Inpatient	563 (31.6)	1415 (27.3)		479 (30.8)	455 (28.1)	
Obesity			0.07889			0.01793
Non-obese	2424 (67.3)	6321 (63.5)		2111 (67.0)	2087 (66.1)	
Obese	1180 (32.7)	3632 (36.5)		1040 (33.0)	1068 (33.9)	
Insurance Type			0.01732			0.03314
Medicare	2946 (89.2)	8175 (89.7)		2561 (89.0)	2610 (90.0)	
Non-Medicare	358 (10.8)	939 (10.3)		316 (11.0)	289 (10.0)	
Hypertension	3295 (91.3)	9213 (92.6)	0.04738	2878 (91.2)	2909 (92.2)	0.03877
Diabetes	1916 (53.0)	4714 (47.3)	0.11555	1629 (51.6)	1674 (53.0)	0.02851
Coronary Artery Disease	1777 (49.2)	5355 (53.7)	0.09123	1581 (50.0)	1480 (46.9)	0.06311
Congestive Heart Failure	632 (17.5)	1760 (17.7)	0.00460	542 (17.2)	535 (16.9)	0.00589
Chronic Obstructive Pulmonary Disease	368 (10.2)	2648 (26.6)	0.43303	354 (11.2)	379 (12.0)	0.02471
Chronic Kidney Disease	1936 (53.8)	4480 (45.2)	0.17355	1659 (52.5)	1711 (54.1)	0.03299
Coronary Artery Bypass Graft/Percutaneous Coronary Intervention	1391 (42.1)	4373 (48.0)	0.11888	1248 (43.3)	1187 (41.0)	0.04811

History of Carotid Endarterectomy and Carotid Artery Stent	151 (4.2)	640 (6.5)	0.10123	145 (4.6)	144 (4.6)	0.00151
Prior Major Amputation	84 (2.3)	185 (1.9)	0.3255	71 (2.2)	76 (2.4)	0.01050
Prior Inflow Treatment	299 (8.3)	1795 (18.1)	0.29272	287)9.1)	289 (9.1)	0.00220
Prior Lower Extremity Intervention	1906 (52.7)	6259 (62.8)	0.20446	1711 (54.1)	1688 (53.4)	0.01460
Aspirin	2676 (74.0)	7896 (79.2)	0.12238	2374 (75.1)	2319 (73.4)	0.03982
P2Y12 Inhibitors	1797 (49.7)	5189 (52.0)	0.04671	1603 (50.7)	1492 (47.2)	0.07031
Statin	2564 (70.9)	7869 (78.9)	0.18502	2286 (72.4)	2235 (70.7)	0.03628
Anticoagulation	637 (17.6)	1611 (16.2)	0.03888	541 (17.1)	552 (17.5)	0.00920
Concomitant Endarterectomy	73 (2.0)	487 (4.9)	0.15848	69 (2.2)	61 (1.9)	0.01784
Level of Treatment			0.29338			0.04732
Above knee	2293 (63.4)	7650 (76.7)		2109 (66.7)	2038 (64.5)	
Below knee	1324 (36.6)	2325 (23.3)		1051 (33.3)	1122 (35.5)	
Type of Treatment			0.11093			0.07452
Plain Angioplasty	1318 (36.9)	3292 (33.7)		1133 (35.9)	1174 (37.2)	

Stent	1198 (33.6)	3581 (36.6)		1092 (34.6)	1077 (34.1)	
Atherectomy	786 (22.0)	1976 (20.2)		692 (21.9)	620 (19.6)	
Stent and Angioplasty	267 (7.5)	934 (9.5)		243 (7.7)	289 (9.1)	
Discharge Aspirin	2875 (80.0)	8307 (83.6)	0.09232	2559 (81.0)	2524 (79.9)	0.02729
Discharge P2Y12 Inhibitors	2645 (73.6)	8141 (81.9)	0.19981	2375 (75.2)	2334 (73.9)	0.02977
Discharge Statin	2715 (75.6)	7773 (78.2)	0.06197	2418 (76.5)	2424 (76.7)	0.00449
Discharge Anticoagulation	713 (19.9)	1818 (18.3)	0.03990	610 (19.3)	627 (19.8)	0.01356

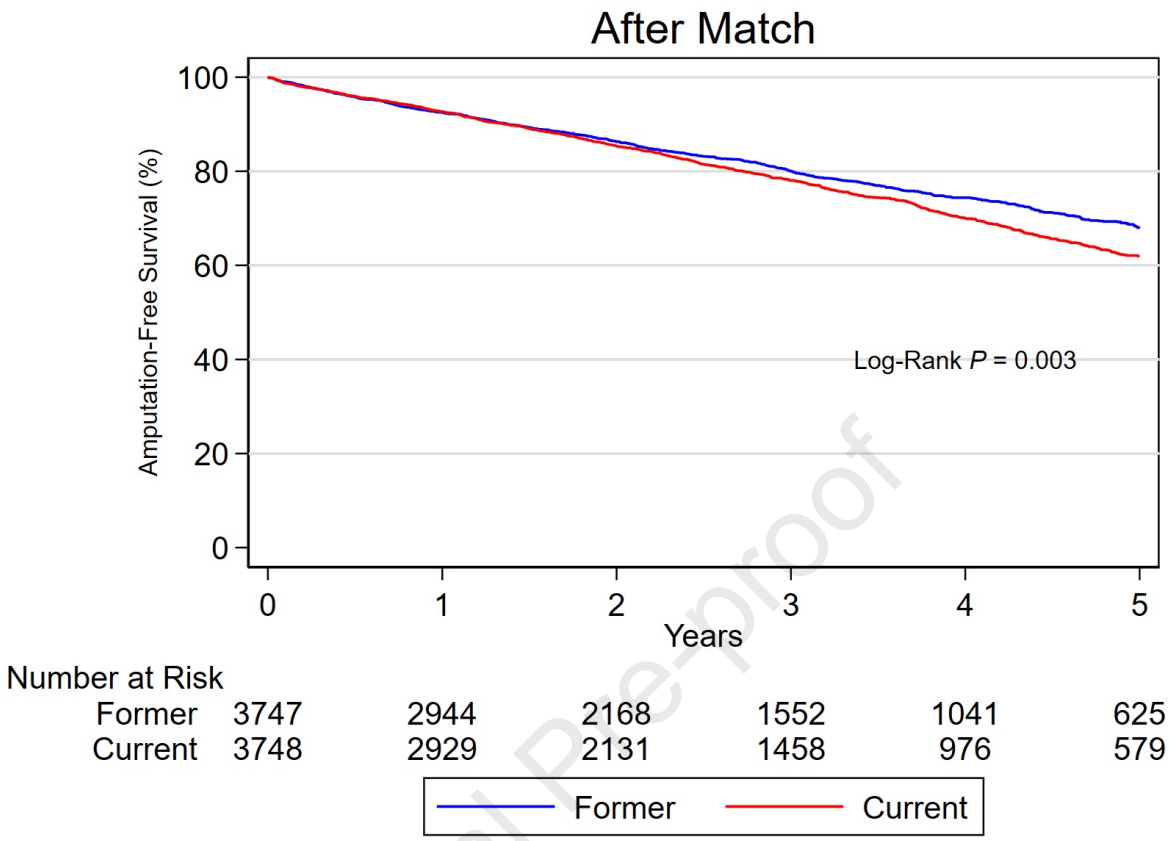
Table III: Five-Year Outcomes Before and After Matching

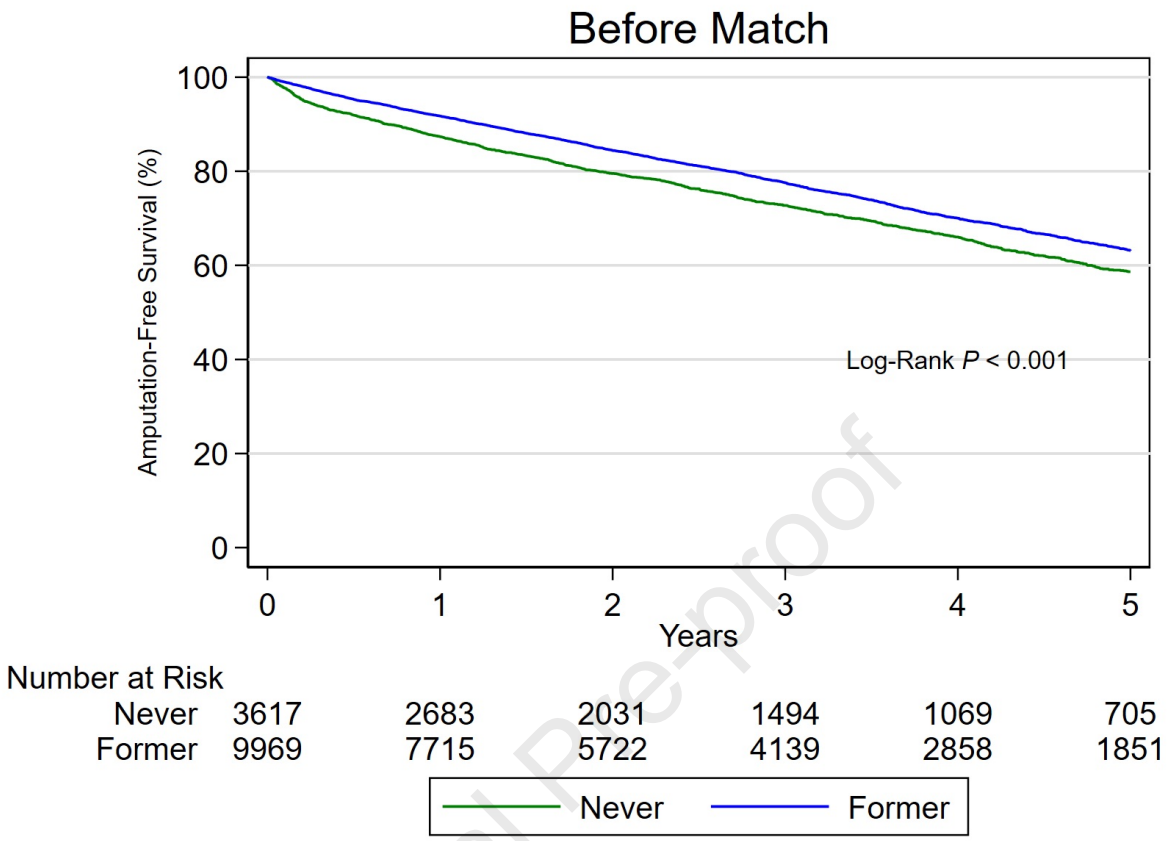
Before Match						
	Former Smokers (FS) N=9,975 (66.0%)	**Current Smokers (CS) N=5,134 (34.0%)**	Log Rank P-Value	**Never Smokers (NS) N=3,617 (26.6%)**	**Former Smokers (FS) N=9,975 (74.4%)**	Log Rank P-Value
	% (95% CI)	% (95% CI)		% (95% CI)	% (95% CI)	
Overall Survival	65.5 (0.64-0.67)	67.1 (0.65-0.69)	0.005	62.0 (0.60-0.64)	65.5 (0.64-0.67)	<0.001
Freedom from Reintervention	48.0 (0.47-0.49)	49.6 (0.48-0.51)	0.035	48.4 (0.46-0.51)	48.0 (0.47-0.49)	0.863
Limb Salvage	94.4 (0.94-0.95)	93.3 (0.93-0.94)	0.051	91.6 (0.90-0.93)	94.4 (0.94-0.95)	<0.001
Amputation-Free Survival	63.1 (0.62-0.64)	64.1 (0.62-0.66)	0.065	58.7 (0.56-0.61)	63.1 (0.62-0.64)	<0.001
After Match						
	Former Smokers (FS) N=3,750 (50.0%)	**Current Smokers (CS) N=3,750 (50.0%)**	Log Rank P-Value	**Never Smokers (NS) N=3,160 (50.0%)**	**Former Smokers (FS) N=3,160 (50.0%)**	
	% (95% CI)	% (95% CI)		% (95% CI)	% (95% CI)	
Overall Survival	70.9 (0.69-0.73)	64.4 (0.62-0.67)	0.002	63.0 (0.61-0.65)	63.3 (0.61-0.66)	0.261

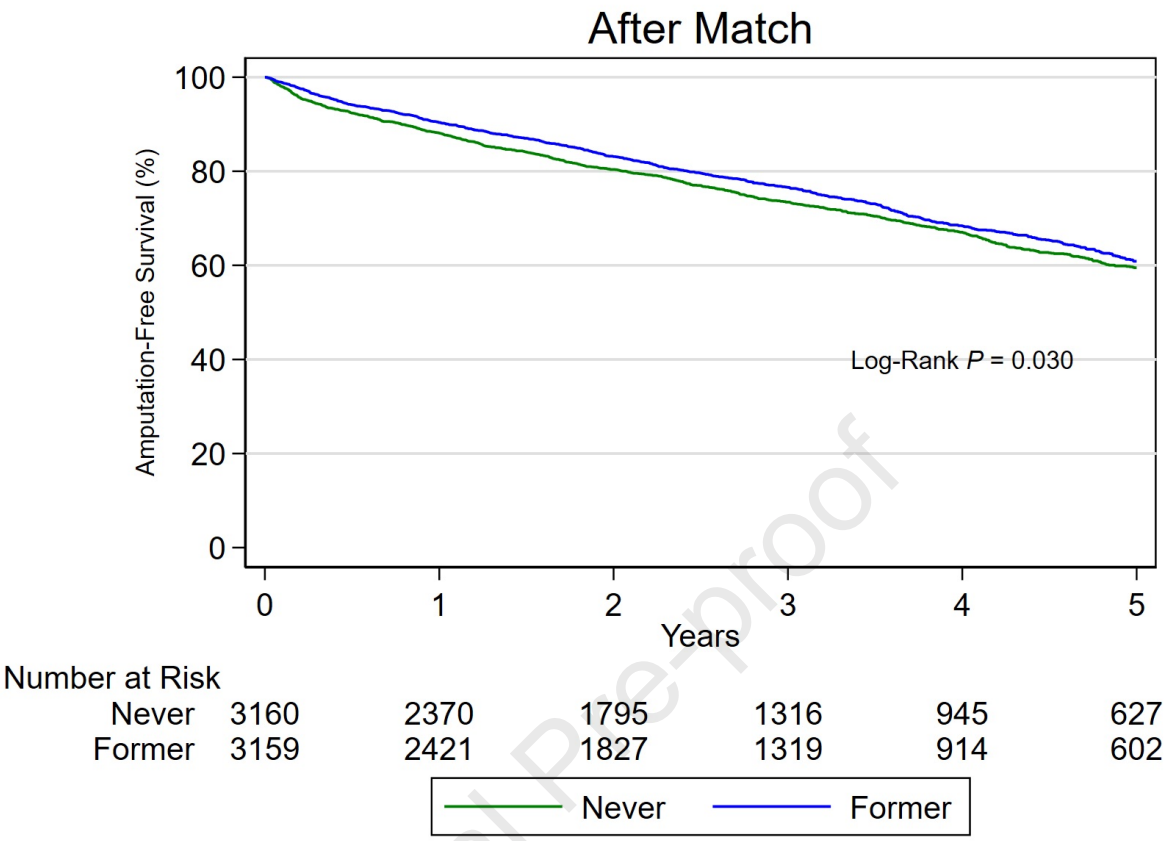
Freedom from Reintervention	47.7 (0.46-0.50)	50.7 (0.48-0.53)	0.003	48.3 (0.46-0.51)	50.5 (0.48-0.53)	0.361
Limb Salvage	94.1 (0.93-0.95)	93.7 (0.93-0.95)	0.265	91.7 (0.90-0.93)	94.4 (0.93-0.95)	<0.001
Amputation-Free Survival	68.0 (0.66-0.70)	62.0 (0.60-0.64)	0.003	59.5 (0.57-0.62)	60.9 (0.58-0.63)	0.030

Table IV: Cox-Regression for Five-Year Outcomes

Current vs. Former Smokers	**Before Match**		**After Match**	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value
All-Cause Mortality	0.90 (0.83-0.98)	0.016	1.18 (1.04-1.33)	0.010
Reintervention	0.94 (0.89-1.00)	0.068	0.89 (0.83-0.96)	0.003
Major Amputation	1.18 (0.95-1.47)	0.129	1.14 (0.87-1.51)	0.346
Major Amputation or Death	0.94 (0.86-1.01)	0.109	1.16 (1.03-1.31)	0.013
Former vs. Never Smokers	**Before Match**		**After Match**	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value
All-Cause Mortality	0.85 (0.77-0.95)	0.003	0.94 (0.82-1.09)	0.426
Reintervention	1.01 (0.94-1.07)	0.875	0.96 (0.89-1.04)	0.352
Major Amputation	0.57 (0.47-0.70)	<0.001	0.66 (0.52-0.84)	0.001
Major Amputation or Death	0.80 (0.73-0.89)	<0.001	0.90 (0.79-1.03)	0.115







Legends

Figure I: Amputation Free Survival in Former versus Current Smokers undergoing Peripheral Vascular Intervention

A: Prior to Matching

B: After Matching

Figure II: Amputation Free Survival in Never versus Former Smokers undergoing Peripheral Vascular Intervention

A: Prior to Matching

B: After Matching