Journal of the American Heart Association

ORIGINAL RESEARCH

Cardiovascular and Limb Events Following Endovascular Revascularization Among Patients ≥65 Years Old: An American College of Cardiology PVI Registry Analysis

E. Hope Weissler, MD, MHS; Yongfei Wang, MS; Jordan M. Gales, MD; Dmitriy N. Feldman, MD; Shipra Arya, MD, SM; Eric A. Secemsky, MD, MSc; Herbert D. Aronow, MD, MPH; Beau M. Hawkins, MD; J. Antonio Gutierrez, MD; Manesh R. Patel, MD; Jeptha P. Curtis, MD; W. Schuyler Jones, MD; Rajesh V. Swaminathan, MD

BACKGROUND: We aimed to characterize the occurrence of major adverse cardiovascular and limb events (MACE and MALE) among patients with peripheral artery disease (PAD) undergoing peripheral vascular intervention (PVI), as well as associated factors in patients with chronic limb threatening ischemia (CLTI).

METHODS AND RESULTS: Patients undergoing PVI in the American College of Cardiology's (ACC) National Cardiovascular Data Registry's PVI Registry who could be linked to Centers for Medicare and Medicaid Services data were included. The primary outcomes were MACE, MALE, and readmission within 1 month and 1 year following index CLTI-PVI or non-CLTI-PVI. Cox proportional hazards regression was used to identify factors associated with the development of the primary outcomes among patients undergoing CLTI-PVI. There were 1758 (49.7%) patients undergoing CLTI-PVI and 1779 (50.3%) undergoing non-CLTI-PVI. By 1 year, MACE occurred in 29.5% of patients with CLTI (n=519), and MALE occurred in 34.0% of patients with CLTI (n=598). By 1 year, MACE occurred in 8.2% of patients with non-CLTI (n=146), and MALE occurred in 26.1% of patients with non-CLTI (n=465). Predictors of MACE at 1 year in CLTI-PVI included end-stage renal disease on hemodialysis, congestive heart failure, prior CABG, and severe lung disease. Predictors of MALE at 1 year in CLTI-PVI included treatment of a prior bypass graft, profunda femoral artery treatment, end-stage renal disease on hemodialysis, and treatment of a previously treated lesion.

CONCLUSIONS: Patients ≥65 years old undergoing PVI experience high rates of MACE and MALE. A range of modifiable and non-modifiable patient factors, procedural characteristics, and medications are associated with the occurrence of MACE and MALE following CLTI-PVI.

Key Words: chronic limb-threatening ischemia ■ endovascular revascularization ■ lower extremity revascularization ■ peripheral artery disease ■ peripheral vascular intervention

See Editorial by xxxx.

Endovascular peripheral vascular intervention (PVI) has become an increasingly common revascularization approach among patients with peripheral artery disease (PAD).[1] Certain characteristics have been demonstrated to confer higher risk of major adverse cardiovascular events (MACE) or major adverse limb events (MALE) following PVI, such as diabetes,[2–4] chronic kidney disease (CKD),[5,6] concomitant coronary

Correspondence to: E. Hope Weissler, MD, DUMC Box 2834, Durham, NC 27701. Email: hope.weissler@duke.edu

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.024279

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Patients with peripheral artery disease are at increased risk for cardiovascular and limb events especially in the peri-procedural period, but high event rates are not limited to patients with the most severe manifestations of peripheral artery disease (ie, chronic limb threatening ischemia) and instead are seen in patients with less severe peripheral artery disease as well.

What Are the Clinical Implications?

- Certain medications (including antiplatelet agents, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins) prescribed at discharge were among the only modifiable associated factors, but prescription of those medications was low.
- This analysis suggests that using registry or claims data to track post-peripheral vascular intervention medication prescriptions and cardiovascular and limb events may help institutions to guide interventions to improve care and prevent these outcomes.

Nonstandard Abbreviations and Acronyms

CLTI	chronic limb threatening ischemia
CMS	Centers for Medicare and Medicaid Services
MACE	major adverse cardiovascular events
MALE	major adverse limb events
NCDR	National Cardiovascular Data Registry
PVI	peripheral vascular intervention

artery or cerebrovascular disease,[7,8] and certain lesion characteristics.[2,9–11] However, the relationships between these factors have not been well explored in high-quality, multi-center data sets, with most reports focusing instead on the contribution of isolated high-risk features to outcomes.[3,4,6,9–11] Other studies have described contributions of multiple risk factors, though with limited outcomes, single center data, or with minimal PAD- and procedure-specific data.[5,12–15] This can lead to attributing risk to a comorbidity (eg, diabetes) while missing the possible intermediary steps by which that characteristic may contribute to events (for example, through the association between diabetes and worse infrapopliteal runoff). While many risk factors for post-PVI MACE or MALE may not be modifiable, a better understanding of risk factors can help with counseling, peri-procedural planning, and post-treatment follow-up. We aimed to more comprehensively describe treatment patterns, the occurrence of MACE, MALE, and associated factors among patients with Medicare undergoing PVI using the NCDR (National Cardiovascular Data Registry's) PVI Registry.

METHODS

Cohort Identification and Linkage to CMS Outcomes

The NCDR PVI Registry collects data about the procedures and patients undergoing percutaneous treatment for PAD at participating institutions with deterministic linkage to Centers for Medicare and Medicaid Services (CMS) outcomes available for patients enrolled in fee-for-service Medicare. The data used in this analysis cannot be made available because of CMS and NCDR data use agreements.

Cohort Identification

There were 13 592 patients who underwent lower extremity PVI between January 01, 2015 and June 30, 2017 (Figure 1). An end date of June 30, 2017 was chosen to ensure adequate follow-up given the CMS data available for linkage. Of these patients, 10 were excluded because they had previously undergone PVI during the same admission, 795 were excluded for

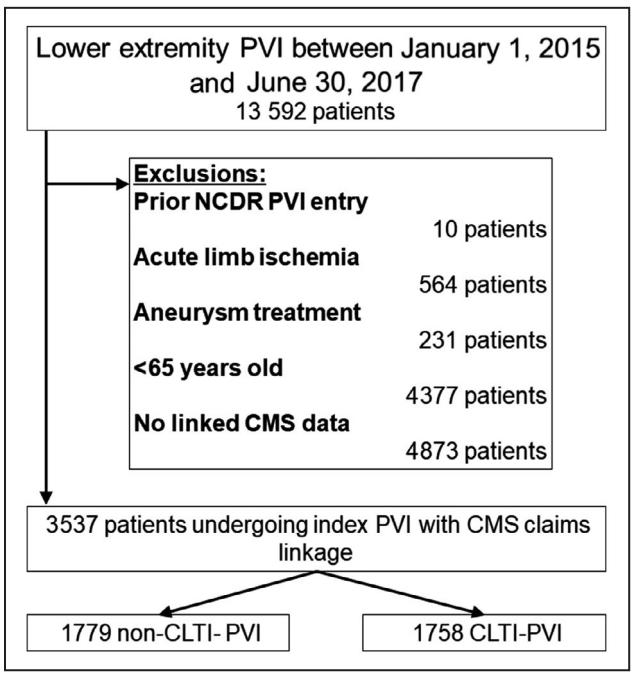

Figure 1. Cohort construction.
CLTI indicates chronic limb threatening ischemia; CMS, Centers for Medicare and Medicaid; NCDR, National Cardiovascular Data Registry; and PVI, peripheral vascular intervention.

undergoing treatment of acute limb ischemia or aneurysms, 4377 were excluded because they were <65 years old, and 4873 were excluded because they could not be linked to CMS claims. This left 3537 patients for analysis. Patients were divided into those undergoing PVI for chronic limb threatening ischemia (CLTI-PVI) and those undergoing PVI for indications other than CLTI (non-CLTI-PVI).

Outcome and Covariate Definitions

The primary outcomes of interest were MACE (all-cause mortality, non-fatal stroke, and non-fatal myocardial infarction [MI]), MALE (major (above ankle) amputation, repeat intervention, or acute limb ischemia), the components of MACE and MALE, and readmission within 1 month and 1 year following index CLTI-PVI or non-CLTI-PVI. These outcomes were ascertained using NCDR PVI data for in-hospital events and CMS inpatient and outpatient claims for post-hospital events using diagnosis and procedure codes. NCDR PVI in-hospital mortality is self-reported by participating institutions. Because laterality was not included in CMS procedure coding until the transition to *International Classification of Diseases, Tenth Revision (ICD-10)* codes part of the way through the study period, we were not able to determine whether subsequent interventions or amputations were on the ipsilateral or contralateral side until that point. Therefore, all major amputations were included as major amputations and all subsequent interventions were considered repeat interventions. A supplemental analysis was done to establish the proportion of major amputations that were ipsilateral once lateralizing codes became available and to model factors associated with ipsilateral amputation-only MALE among those patients. It was not possible to determine whether amputations or repeat interventions were planned or unplanned. Because repeat interventions were ascertained primarily from procedure codes, it was not possible to determine whether they were repeat interventions on the same lesion(s) treated during the index PVI or not.

Covariates were defined as per the NCDR Data Dictionary, available online, and included sociodemographics, comorbidities, PAD characteristics, and procedural characteristics. Procedural success was defined as completed lesion treatment with final stenosis <50% in the absence of thrombosis, embolism, significant dissection, perforation, vascular complications requiring treatment, or unplanned vascular intervention. Medications at discharge were taken from NCDR PVI data.

Statistical Analysis

Descriptive analyses and outcome rates were stratified by PVI type (CLTI and non-CLTI). Baseline characteristics and observed outcomes were described with categorical variables presented as frequencies (percentages) and continuous variables presented as medians (interquartile range) or means (SD). Mortality was calculated using Kaplan–Meier methods. Rates of other events were calculated using the cumulative incidence function to account for the competing risk of mortality using the Fine-Gray method.[16] Per CMS guidelines, neither frequency values <11 nor other values that could be used to calculate a value <11 were reported, except 0.

Associations between patient, PAD, and procedural characteristics and outcomes (MACE, MALE, readmission, and mortality) were analyzed for patients undergoing CLTI-PVI using Cox proportional hazards regression. Factors associated with outcomes among patients with non-CLTI-PVI were not analyzed because of the relatively few events among patients with non-CLTI-PVI. Candidate variables were selected based on clinical experience and prior literature and included demographics, comorbidities, PAD characteristics (Rutherford classification, number of patent runoff vessels), procedural factors (number of treated lesions, arterial segments treated, re-treatment of previously treated lesions, chronic total occlusion treatment, atherectomy use, procedural success), and medications at discharge. Ankle-brachial indices (ABIs), toe pressure, and infrapopliteal runoff could not be included in the risk models because of missing data. Backward elimination stepwise regression was performed to identify the best model.

A P value threshold of <0.05 was used to define statistical significance. All analyses were done using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina). The Human Investigation Committee of the Yale University School of Medicine approved the use of the PVI Registry data for research purposes. Informed consent was not required for this study.

RESULTS

Baseline and Procedural Characteristics

Between January 1, 2015 and December 31, 2017, 3537 patients underwent PVI procedures meeting inclusion criteria. Of these, 1758 (49.7%) were done for an indication of CLTI (CLTI-PVI) and 1779 were not (50.3%, non-CLTI-PVI). Patients with CLTI-PVI were older than patients with non-CLTI-PVI (77.3±8.1 and 74.0±6.4 years, respectively). Most patients undergoing CLTI-PVI had tissue loss and/or gangrene (n=1304, 74.2%) while most patients undergoing non-CLTI-PVI had severe claudication (n=1309, 73.6%, Table 1). Only half of the cohort overall had minimum resting ABIs available (CLTI: n=758, 43.1%; non-CLTI: n=999, 56.2%) and the mean among patients with CLTI-PVI was 0.61±0.34 while among patients with non-CLTI-PVI it was 0.62±0.24. Toe pressures were available in 15% of

Table 1. Baseline Characteristics of Patients Receiving CLTI-PVI and Non-CLTI-PVI

	Total, n (%) 3537	CLTI, n (%) 1758 (49.7%)	Non-CLTI, n (%) 1779 (50.3%)
Demographics and comorbidities			
Male	2054 (58.1)	1001 (56.9)	1053 (59.2)
White	3028 (85.6)	1422 (80.9)	1606 (90.3)
Current smoking	924 (26.1)	346 (19.7)	578 (32.5)
Coronary artery disease	1989 (56.2)	947 (53.9)	1042 (58.6)
Family history of coronary artery disease	407 (11.5)	171 (9.7)	236 (13.3)
Prior coronary artery bypass graft	960 (27.1)	466 (26.5)	494 (27.8)
Prior myocardial infarction	825 (23.3)	422 (24.0)	403 (22.7)
Prior congestive heart failure	739 (20.9)	476 (27.1)	263 (14.8)
Cerebrovascular disease	1100 (31.1)	529 (30.1)	571 (32.1)
Diabetes	1845 (52.2)	1063 (60.5)	782 (44.0)
End-stage renal disease on hemodialysis	255 (7.2)	212 (12.1)	43 (2.4)
Severe lung disease*	589 (16.7)	264 (15.0)	325 (18.3)
Hypertension	3285 (92.9)	1616 (91.9)	1669 (93.8)
Dyslipidemia	2922 (82.6)	1349 (76.7)	1573 (88.4)
PAD characteristics			
PAD severity			
Asymptomatic or atypical claudication	146 (4.1)		146 (8.2)
Rutherford 1	65 (1.8)		65 (3.7)
Rutherford 2	259 (7.3)		259 (14.6)
Rutherford 3	1309 (37.0)		1309 (73.6)
Rutherford 4	454 (12.8)	454 (25.8)	
Rutherford 5/6	1304 (36.9)	1304 (74.2)	
Prior PAD intervention	1373 (38.8)	580 (33.0)	793 (44.6)
Procedural characteristics			
Elective procedure	3027 (85.6)	1229 (73.9)	1728 (97.1)
Lesion location, artery			
Iliac	924 (26.1)	287 (16.3)	637 (35.8)
Common femoral	239 (6.8)	103 (5.9)	136 (7.6)
Superficial femoral	1878 (53.1)	886 (50.4)	992 (55.8)
Profunda femoral	52 (1.5)	21 (1.2)	31 (1.7)
Popliteal	1007 (28.5)	617 (35.1)	390 (21.9)
Tibial	1062 (30.0)	856 (48.7)	206 (11.6)
Pedal	58 (1.6)	54 (3.1)	--
Bypass graft	93 (2.6)	31 (1.8)	62 (3.5)
Lesion length, mm, mean (SD)	103.8 (93.7)	117.5 (102.2)	90.9 (82.9)
Patent runoff vessels			
2 or 3	1670 (47.2)	687 (39.1)	983 (55.3)
0 or 1	750 (21.2)	561 (31.9)	189 (10.6)
Missing	1117 (31.6)	510 (28.7)	607 (34.1)
Previously treated lesion	541 (15.3)	218 (12.4)	323 (18.2)
Chronic total occlusion	1163 (32.9)	710 (40.4)	453 (25.5)
Atherectomy usage	992 (28.1)	518 (29.5)	474 (26.6)
Procedural success†	3129 (88.5)	1529 (87.0)	1600 (89.9)
Length of stay			
0 d	1683 (47.6)	668 (38.0)	1015 (57.1)
1 d	1050 (29.7)	436 (24.8)	614 (34.5)
≥2 d	804 (22.7)	654 (37.2)	150 (8.4)

Per Centers for Medicare and Medicaid guidelines, cells with values <11 are suppressed (--). CLTI indicates chronic limb threatening ischemia; PAD, peripheral artery disease; and PVI, peripheral vascular intervention.

*Severe lung disease: Home O_2 therapy, forced expiratory velocity <50% of predicted with forced expiratory velocity 1<forced vital capacity<0.70, or diffusion capacity of the lungs for carbon monoxide <40%.

†Procedural success: completed lesion treatment with final stenosis <50% without thrombosis, embolism, significant dissection, perforation, vascular complications requiring treatment, or unplanned vascular intervention.

the overall cohort (CLTI-PVI: n=281, 16.0%; non-CLTI-PVI: n=248, 13.9%) and the mean among patients with CLTI-PVI was 48.3±32.4 mm Hg while among patients with non-CLTI-PVI it was 65.6±30.3 mm Hg.

Most procedures were elective (CLTI-PVI: n=1229, 73.9%; non-CLTI-PVI: n=1728, 97.1%). The average number of lesions treated was 1.69±0.91 overall (1.81±0.98 in CLTI-PVI and 1.57±0.83 in non-CLTI-PVI). Procedural success was achieved in 87.0% of CLTI-PVI (n=1529) and 89.9% of non-CLTI-PVI (n=1600). Patients with CLTI-PVI were usually discharged on the same day (n=668, 38.0%) or the next day (n=436, 24.8%), but 37.2% stayed for ≥2 days (n=654), while patients with non-CLTI-PVI were predominantly discharged on the same day (n=1015, 57.1%), with 34.5% discharged the following day (n=614). The most commonly prescribed medications were antiplatelet agents, prescribed for 87.8% of patients with CLTI-PVI (n=1543) and 96.2% of non-CLTI-PVI (n=1712) at discharge. Statins were the second most commonly prescribed medications (CLTI-PVI: n=1158, 65.9%, non-CLTI-PVI: n=1411, 79.3%, Table 2).

Non-CLTI-PVI Outcomes

Among patients with non-CLTI-PVI, 6.8% were readmitted within 30 days of index PVI (n=120, Table 3). MALE

Table 2. Medication Prescription at Discharge

	CLTI, n (%) 1758 (49.7%)	Non-CLTI, n (%) 1779 (50.3%)
Antiplatelets	1543 (87.8)	1712 (96.2)
Statins	1158 (65.9)	1411 (79.3)
β-blockers	1069 (60.8)	1073 (60.3)
Angiotensin-converting enzyme inhibitors	564 (32.1)	709 (39.9)
Angiotensin-II receptor blockers	266 (15.1)	368 (20.7)
Non-statin lipid lowering therapies	121 (6.9)	190 (10.7)
Warfarin	249 (14.2)	118 (6.6)
Direct oral anticoagulation	154 (8.8)	103 (5.8)
Apixaban	74 (4.2)	48 (2.7)
Rivaroxaban	51 (2.9)	36 (2.0)

CLTI indicates chronic limb threatening ischemia.

occurred among 8.4% of patients (n=150), including 7.5% undergoing repeat revascularizations (n=133) and 1.1% experiencing acute limb ischemia (n=20). MACE occurred among 1.0% of patients by 30 days (n=17). By 1 year, 37.9% of patients with non-CLTI-PVI had been readmitted (n=674). MALE occurred among 26.1% of patients (n=465) by 1 year, including 25.1% undergoing repeat revascularization (n=447) and 1.6% suffering acute limb ischemia (n=29). MACE occurred among 8.2% of patients (n=146), including deaths in 5.3% (n=95), MIs in 2.5% (n=45), and strokes in 1.4% (n=25).

CLTI-PVI Outcomes

Readmission occurred among 20.0% of patients with CLTI-PVI within 30 days (n=352, Table 2). MALE occurred among 11.4% of patients (n=200) by 30 days, including repeat revascularizations in 7.2% (n=127) and major amputations in 4.5% (n=79). MACE occurred by 30 days among 5.1% of patients (n=90), primarily in the form of all-cause mortality (4.3%, n=76). By 1 year, 61.7% of patients with CLTI-PVI had been readmitted (n=1084). MALE occurred among 34.0% of patients (n=598) by 1 year, including repeat revascularizations in 25.5% (n=449), major amputations in 12.7% (n=224), and acute limb ischemia in 1.3% (n=22). Among patients with CLTI-PVI discharged after lateralizing *ICD-10* codes became available, 82.4% of major amputations were ipsilateral (Table S1). MACE occurred among 29.5% of patients with CLTI-PVI (n=519), including death in 26.3% (n=463), MIs in 3.5% (n=62), and strokes in 1.6% (n=28) by 1 year.

Factors Predicting MACE, MALE, and Readmission Among Patients With CLTI-PVI at 1 Year

In a multivariable model, end-stage renal disease (ESRD) on hemodialysis was associated with the greatest increased likelihood of MACE (adjusted hazard ratio [HR_{adj}], 2.67; 95% CI, 2.12–3.37; $P<0.001$; Table 4). Congestive heart failure, prior coronary artery bypass grafting, severe lung disease, cerebrovascular disease, and male sex were also associated with 1-year MACE. Antiplatelet, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and statin

Table 3. Thirty-Day and 1-Year Outcomes

	Non-CLTI PVI		CLTI PVI	
	30 d, n (%)	1 y, n (%)	30 d, n (%)	1 y, n (%)
MACE	17 (1.0)	146 (8.2)	90 (5.1)	519 (29.5)
All-cause mortality	--	95 (5.3)	76 (4.3)	463 (26.3)
Myocardial infarction	--	45 (2.5)	12 (0.7)	62 (3.5)
Ischemic stroke	--	25 (1.4)	<10*	28 (1.6)
MALE	150 (8.4)	465 (26.1)	200 (11.4)	598 (34.0)
Repeat revascularization	133 (7.5)	447 (25.1)	127 (7.2)	449 (25.5)
Major amputation	0	--	79 (4.5)	224 (12.7)
Acute limb ischemia	20 (1.1)	29 (1.7)	12 (0.7)	22 (1.3)
Readmission	120 (6.8)	674 (37.9)	352 (20.0)	1084 (61.7)

Per Centers for Medicare and Medicaid guidelines, cells with values <11 are suppressed (--). CLTI indicates chronic limb threatening ischemia; MACE, major adverse cardiovascular events; MALE, major adverse limb events; and PVI, peripheral vascular intervention.

Table 4. Factors Associated with MACE by 1 Year Among Patients With CLTI-PVI

	HR (95% CI)	*P* value
Age, y	1.04 (1.03–1.06)	<0.001
End-stage renal disease on hemodialysis	2.67 (2.12–3.37)	<0.001
Severe lung disease	1.34 (1.06–1.69)	0.013
Congestive heart failure	1.71 (1.42–2.05)	<0.001
Prior coronary artery bypass graft	1.47 (1.20–1.80)	<0.001
Family history of coronary artery disease	0.59 (0.41–0.85)	0.004
Rutherford 4 PAD	0.80 (0.64–1.00)	0.046
Procedural success	0.76 (0.60–0.96)	0.023
Previous lesion treatment	0.70 (0.52–0.96)	0.025
Male sex	1.22 (1.02–1.47)	0.033
Cerebrovascular disease	1.23 (1.02–1.48)	0.028
Antiplatelet at discharge	0.61 (0.48–0.77)	<0.001
Angiotensin-converting enzyme inhibitor at discharge	0.76 (0.62–0.92)	0.007
Angiotensin II receptor blocker at discharge	0.72 (0.54–0.95)	0.022
Statin at discharge	0.73 (0.60–0.88)	<0.001

CLTI indicates chronic limb threatening ischemia; HR, hazard ratio; MACE, major adverse cardiovascular events; PAD, peripheral artery disease; and PVI, peripheral vascular intervention.

use at discharge were associated with lower likelihood of MACE.

Within 1 year, treatment of a bypass graft (HR_{adj}, 2.07; 95% CI, 1.30–3.31; *P*=0.002; Table 5) or the profunda femoral artery (HR_{adj}, 1.94; 95% CI, 1.09–3.47; *P*=0.025) were associated with the greatest increased likelihood of MALE. ESRD on hemodialysis and treatment of a previously treated lesion was also associated with 1-year MALE. Procedural success was associated with lower likelihood of MALE. Similar factors were associated with ipsilateral amputation-only MALE among patients discharged after lateralizing *ICD-10* codes became available, except that treatment of the profunda femoral artery and prior lesion treatment were no longer significant (Table S2).

Readmission within 1 year was associated with antiplatelet use at discharge (Figure 2), warfarin use at discharge, ESRD on hemodialysis, and diabetes. Black race was also independently associated with readmission. Factors associated with mortality within 1 year can be seen in Table S3.

DISCUSSION

We sought to characterize treatment patterns, outcomes, and contributing risk factors among patients with Medicare undergoing PVI in the NCDR PVI registry. Our analysis yielded 3 key findings. First, while a higher proportion of patients with CLTI-PVI experienced major amputation, readmission, and mortality, both CLTI-PVI and patients with non-CLTI-PVI experienced similar rates of MI, stroke, and repeat revascularization. Second, although many of the factors associated with MACE, MALE, and readmission were non-modifiable, a few key factors could be modified by physicians. Third, the prescription of PAD guideline-based medical treatments at discharge was relatively low: though not a novel finding, this bears emphasis especially given that certain medications were associated with lower MACE and readmission in our analysis.

It is generally acknowledged that the risks of MACE and MALE are lower among PAD patients without CLTI.[17] While the purpose of our analysis was not to compare event rates between CLTI-PVI and non-CLTI-PVI patients, our findings challenge the common assumptions about CLTI and non-CLTI event rates. Patients undergoing CLTI-PVI were clearly at higher risk for mortality, major amputation, and readmission within both 30 days and 1 year. However, patients had similar rates of reintervention following CLTI-PVI and non-CLTI-PVI within 30 days and 1 year (7.2% and 25.5%, respectively in CLTI-PVI; 7.5% and 25.1% in non-CLTI-PVI). It was not possible to establish whether repeat interventions were on the same lesion (or even on the same side during the period of *ICD-9* codes) or whether they were planned in advance of the index PVI; therefore, it is possible that some of these apparent reinterventions represented planned staged treatment of complex or bilateral disease. Though less common, 1-year rates of MI, stroke, and acute limb ischemia were also relatively similar between patients with CLTI-PVI and non-CLTI-PVI (3.5%, 1.6%, and 1.3%, respectively, in CLTI-PVI; 2.5%, 1.4%, and 1.6% in non-CLTI-PVI). Though surprising, the similarities in rates of peri- and post-procedural adverse events

Table 5. Factors Associated With MALE by 1 Year Among Patients With CLTI-PVI

	HR (95% CI)	*P* value
End-stage renal disease on hemodialysis	1.64 (1.31–2.06)	<0.001
Congestive heart failure	0.79 (0.66–0.96)	0.018
Superficial femoral artery treatment	1.21 (1.03–1.43)	0.022
Profunda femoral artery treatment	1.94 (1.09–3.47)	0.025
Bypass graft treatment	2.07 (1.30–3.31)	0.002
Procedural success	0.59 (0.48–0.74)	<0.001
No. of lesions treated	1.13 (1.04–1.22)	0.002
Previously treated lesion	1.45 (1.16–1.80)	<0.001

CLTI indicates chronic limb threatening ischemia; HR, hazard ratio; MALE, major adverse limb events; and PVI, peripheral vascular intervention.

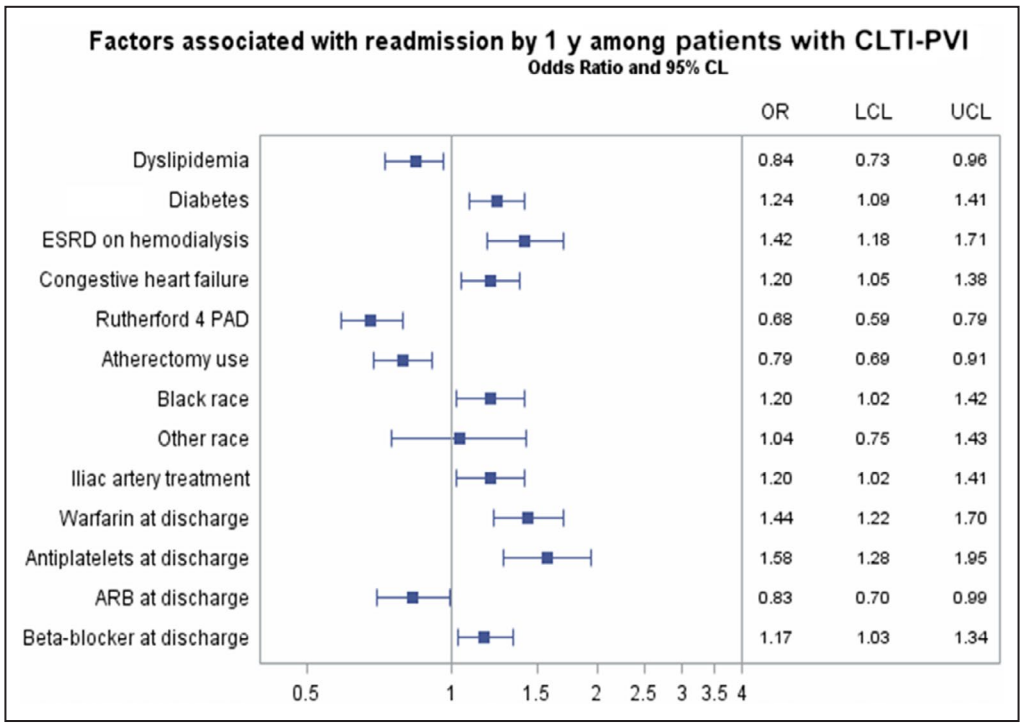

Figure 2. Factors associated with readmission by 1 year among patients with chronic limb threatening ischemia-peripheral vascular intervention.
"Other" race includes Asian, American Indian, and Alaskan Native. ARB indicates angiotensin receptor blocker; CLTI, chronic limb threatening ischemia; ESRD, end-stage renal disease; LCL, lower confidence limit; OR, odds ratio; PAD, peripheral artery disease; PVI, peripheral vascular intervention; and UCL, upper confidence limit.

may be due in part to the slightly higher frequencies of certain factors associated with MACE and MALE among patients with non-CLTI-PVI, such as male sex, severe lung disease, and prior lesion treatment, though other conditions associated with MACE and MALE (eg, diabetes, ESRD) are more common in patients with CLTI-PVI. These data suggest that patients with non-CLTI-PVI cannot be assumed to have lower rates of adverse events on the basis of their PAD severity alone, increasing the importance of patient-centered discussions on risk-benefit tradeoffs to ensure appropriate interventions for only those patients with lifestyle-limiting claudication despite optimal medical therapy.[18,19]

Many of the characteristics associated with higher event rates in our analysis of patients with CLTI-PVI have been previously remarked upon and are not modifiable at the time of PVI, including ESRD on hemodialysis, age, severe lung disease, congestive heart failure, cerebrovascular disease, diabetes, and prior coronary artery bypass grafting.[3,4,6,7,14,20] Factors associated with MALE were primarily related to PAD-specific and procedural characteristics, including superficial and profunda femoral artery treatment, treatment of a bypass graft, number of lesions treated, and re-treatment of a previously treated lesion, while procedural success was protective. Superficial femoral artery intervention may have been associated with MALE by virtue of its relative frequency compared with other sites of intervention. Profunda femoral intervention is likely to occur in situations in which treatment of the superficial femoral artery is not possible, denoting more severe disease. These factors associated with MALE are also largely non-modifiable (other than number of lesions treated), but they may be useful to clinicians in counseling patients pre-PVI and deciding on necessary follow-up post-PVI. We were interested to see that the factors associated with MALE did not change substantially when the model was limited to patients with ipsilateral amputations who were discharged after lateralizing *ICD-10* codes became available (in Table S2). The loss of profunda femoral artery treatment and prior lesion treatment as factors associated with MALE in the more restricted model may be reflective of patterns/severity of disease or of loss of power in the smaller sample. Unfortunately, we were not able to incorporate ABI as a measure of disease severity into the models because of missingness in the case report forms, identifying a possible deviation from guidelines recommending ABI measurements for all patients with PAD.[21–23] Of interest, patients undergoing CLTI-PVI and non-CLTI-PVI had similar mean minimum

ABIs, highlighting the shortcomings of ABIs as a measurement of PAD severity.

Discharge medications were some of the few modifiable factors associated with outcomes. Antiplatelet agents, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins were all associated with lower risks of MACE, consistent with prior reports.[24–30] Unfortunately, <90% of patients with CLTI-PVI were discharged on antiplatelet therapy and only two thirds were discharged on statins. Markedly more patients with non-CLTI-PVI were discharged on antiplatelet agents and statins (96% and 79%, respectively), identifying a risk-treatment paradox where patients at highest risk (CLTI) who would benefit the most are not receiving these medical therapies. Readmissions were higher in patients on antiplatelet or anticoagulants, which may be attributed to bleeding or residual confounding related to greater comorbidities. β-blocker prescriptions at discharge were also associated with greater readmissions in our analysis. Beta-blocker use in PAD has historically been controversial with conflicting data, particularly in patients with CLTI where beta-receptor antagonism through established mechanisms can lead to impaired peripheral perfusion.[15,17,18]

Limitations

This study has several limitations to consider. First, to ascertain outcomes, we were limited to patients with fee-for-service Medicare, leading to exclusion of 9250 patients who were <65 years old or unable to be linked to CMS claims. While some of the risk factors for MACE, MALE, and readmission might differ among younger patients, most patients with PAD are ≥65 years old. Second, it was not possible to tell whether repeat interventions or amputations were planned, or whether repeat interventions were on the index lesion, and outcomes were limited to 1 year because of data availability. Third, missingness of certain data fields precluded their inclusion in models, most notably ABIs. NCDR PVI also does not collect certain data fields such as calcification, reference vessel diameters, lower extremity ulcer characteristics, or the indications for medication prescriptions that may have shed additional light on relationships between comorbidity- and PAD-related risks of clinical events. Fourth, medication associations were based on prescriptions at the time of hospital discharge and may not reflect long-term prescription or adherence. Fifth, although we adjusted for a variety factors in our models, unmeasured confounders may be present. Nevertheless, these model variables still function as markers of risk even if they are not the fundamental drivers of risk. Finally, as this was primarily an exploratory analysis we did not adjust for multiple testing; however, the factors found to be associated with adverse events appeared clinically reasonable.

CONCLUSIONS

The current study, representing a large sample of Medicare patients with PAD in a high-quality national registry, revealed that patients with and without CLTI experience high rates of MACE, MALE, and readmission following PVI. Understanding the relationships between baseline comorbidities, medications at discharge, disease- and procedure-specific characteristics, and outcomes, is critical to patient counseling and treatment planning. These results offer an opportunity to focus on high-quality, longitudinal care of patients with PAD, including patient-clinician shared decision-making, improved medical therapies, and optimal post-intervention surveillance strategies, in the future.

ARTICLE INFORMATION

Received October 28, 2021; accepted February 21, 2022.

Affiliations

Division of Vascular and Endovascular Surgery, Department of Surgery, Duke University School of Medicine, Durham, NC (E.H.W.); Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, CT (Y.W., J.P.C.); Center of Outcome Research and Evaluation, Yale-New Haven Health Services, New Haven, CT (Y.W., J.P.C.); Texas Heart Institute, Houston, TX (J.M.G.); Division of Cardiology, Weill Cornell Medical College, New York, NY (D.N.F.); Division of Vascular and Endovascular Surgery, Stanford University School of Medicine, Palo Alto, CA (S.A.); Division of Cardiology, Beth Israel Deaconess Medical Center, Boston, MA (E.A.S.); Smith Center for Outcomes Research in Cardiology, Boston, MA (E.A.S.); Lifespan Cardiovascular Institute/Alpert Medical School at Brown University, Providence, RI (H.D.A.); Cardiovascular Section, University of Oklahoma Health Sciences Center, Oklahoma, OK (B.M.H.); Division of Cardiology, Duke University Health System, Durham, NC (J.A.G., M.R.P., W.S.J., R.V.S.); and Cardiology Section, Durham VA Medical Center, Durham, NC (J.A.G.).

Sources of Funding

E.H.W. was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number F32HL151181. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH).

Disclosures

E.H.W. receives support from the NIH (award number NHLBI F32HL151181). S.A. receives research support from Veterans Affairs Health Services Research & Development. E.A.S. receives research support from the NIH (award number NIH/NHLBI K23HL150290) as well as from Harvard Medical School's Shore Faculty Development Award, AstraZeneca, BD, Boston Scientific, Cook, CSI, Laminate Medical, Medtronic and Philips. E.A.S. also receives consulting fees from Abbott, Bayer, BD, Boston Scientific, Cook, CSI, Inari, Janssen, Medtronic, Philips, and VentureMed. H.A.D. receives consulting fees from Philips. B.M.H. receives research support from Behring, Hemostemix, and the NIH (NHLBI) as well as consulting fees from Baim Research Institute. A.G. receives consulting fees from Janssen Pharmaceuticals and Amgen. M.R.P. receives research support from the Agency for Healthcare Research and Quality, AstraZeneca, Bayer, Jansen, Procyrion, and Heartflow and sits on the advisory boards of Bayer, Janssen, and AstraZeneca. J.P.C. receives research support from the NIH (NHLBI) and salary support from the American College of Cardiology. W.S.J. receives research support from the Agency for Healthcare Research and Quality, AstraZeneca, American Heart Association, Bristol-Myers Squibb, Doris Duke Charitable Foundation,

and the Patient-Centered Outcomes Research Institute. W.S.J. also receives honoraria/other from Bayer, Bristol-Myers Squibb, and Janssen Pharmaceuticals. R.V.S. receives research support from ACIST Medical and Cardiovascular Systems, Inc, serves on the advisory board of Philips, and receives fees from Medtronic.

Supplemental Material

Tables S1–S3

REFERENCES

1. Goodney PP, Beck AW, Nagle J, Welch HG, Zwolak RM. National trends in lower extremity bypass surgery, endovascular interventions, and major amputations. *J Vasc Surg*. 2009;50:54–60. doi: 10.1016/j.jvs.2009.01.035
2. Bakken AM, Protack CD, Saad WE, Hart JP, Rhodes JM, Waldman DL, Davies MG. Impact of chronic kidney disease on outcomes of superficial femoral artery endoluminal interventions. *Ann Vasc Surg*. 2009;23:560–568. doi: 10.1016/j.avsg.2008.11.010
3. Neupane S, Edla S, Maidona E, Sweet MC, Szpunar S, Davis T, LaLonde TA, Mehta RH, Rosman HS, Yamasaki H. Long-term outcomes of patients with diabetes mellitus undergoing percutaneous intervention for popliteal and infrapopliteal peripheral arterial disease. *Catheter Cardiovasc Interv*. 2018;92:117–123. doi: 10.1002/ccd.27571
4. Shammas AN, Jeon-Slaughter H, Tsai S, Khalili H, Ali M, Xu H, Rodriguez G, Cawich I, Armstrong EJ, Brilakis ES, et al. Major limb outcomes following lower extremity endovascular revascularization in patients with and without diabetes mellitus. *J Endovasc Ther*. 2017;24:376–382. doi: 10.1177/1526602817705135
5. Heideman PP, Rajebi MR, McKusick MA, Bjarnason H, Oderich GS, Friese JL, Fleming MD, Stockland AH, Harmsen WS, Mandrekar J, et al. Impact of chronic kidney disease on clinical outcomes of endovascular treatment for femoropopliteal arterial disease. *J Vasc Interv Radiol*. 2016;27:1204–1214. doi: 10.1016/j.jvir.2016.04.036
6. Kim HO, Kim J-M, Woo JS, Choi D, Ko Y-G, Ahn C-M, Lee S-W, Lee J-H, Choi S-H, Yu CW, et al. Effects of chronic kidney disease on clinical outcomes in patients with peripheral artery disease undergoing endovascular treatment: analysis from the K-VIS ELLA registry. *Int J Cardiol*. 2018;262:32–37. doi: 10.1016/j.ijcard.2018.03.108
7. Krishnamurthy V, Munir K, Rectenwald JE, Mansour A, Hans S, Eliason JL, Escobar GA, Gallagher KA, Grossman PM, Gurm HS, et al. Contemporary outcomes with percutaneous vascular interventions for peripheral critical limb ischemia in those with and without poly-vascular disease. *Vasc Med*. 2014;19:491–499. doi: 10.1177/1358863X14552013
8. van Kuijk JP, Flu WJ, Welten GM, Hoeks SE, Chonchol M, Vidakovic R, Verhagen HJ, Bax JJ, Poldermans D. Long-term prognosis of patients with peripheral arterial disease with or without polyvascular atherosclerotic disease. *Eur Heart J*. 2010;31:992–999. doi: 10.1093/eurheartj/ehp553
9. de Athayde SR, Matielo MF, Brochado Neto FC, Pires APM, de Almeida RD, de Jesus MM, Sacilotto R. Impact of calcification and infrapopliteal outflow on the outcome of endovascular treatment of femoropopliteal occlusive disease. *JRSM Cardiovasc Dis*. 2019;8:2048004019828941. doi: 10.1177/2048004019828941
10. Park UJ, Kim HT, Roh YN. Impact of tibial runoff on outcomes of endovascular treatment for femoropopliteal atherosclerotic lesions. *Vasc Endovasc Surg*. 2018;52:498–504. doi: 10.1177/1538574418779466
11. Watanabe Y, Hozawa K, Hiroyoshi K, Naganuma T, Ishiguro H, Nakamura S. The importance of patency of tibial run off arteries on clinical outcomes after stenting for chronic total occlusions in the superficial femoro-popliteal artery. *Eur J Vasc Endovasc*. 2018;56:857–863. doi: 10.1016/j.ejvs.2018.08.001
12. Axley JC, McFarland GE, Novak Z, Scali ST, Patterson MA, Pearce BJ, Spangler EL, Passman MA, Beck AW. Factors associated with amputation after peripheral vascular intervention for intermittent claudication. *Ann Vasc Surg*. 2020;62:133–141. doi: 10.1016/j.avsg.2019.08.073
13. Bodewes TC, Soden PA, Ultee KH, Zettervall SL, Pothof AB, Deery SE, Moll FL, Schermerhorn ML. Risk factors for 30-day unplanned readmission following infrainguinal endovascular interventions. *J Vasc Surg*. 2017;65:484–494.e3. doi: 10.1016/j.jvs.2016.08.093
14. Simons JP, Goodney PP, Flahive J, Hoel AW, Hallett JW, Kraiss LW, Schanzer A; Society for Vascular Surgery Vascular Quality I. A comparative evaluation of risk-adjustment models for benchmarking amputation-free survival after lower extremity bypass. *J Vasc Surg*. 2016;63:990–997. doi: 10.1016/j.jvs.2015.09.051
15. Liang P, Li C, O'Donnell TFX, Lo RC, Soden PA, Swerdlow NJ, Schermerhorn ML. In-hospital versus postdischarge major adverse events within 30 days following lower extremity revascularization. *J Vasc Surg*. 2019;69:482–489. doi: 10.1016/j.jvs.2018.06.207
16. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509. doi: 10.2307/2670170
17. Conte MS. Diabetic revascularization: endovascular versus open bypass–do we have the answer? *Semin Vasc Surg*. 2012;25:108–114. doi: 10.1053/j.semvascsurg.2012.04.004
18. Baumgartner I, Norgren L, Fowkes FGR, Mulder H, Patel MR, Berger JS, Jones WS, Rockhold FW, Katona BG, Mahaffey K, et al. Cardiovascular outcomes after lower extremity endovascular or surgical revascularization: the EUCLID trial. *J Am Coll Cardiol*. 2018;72:1563–1572. doi: 10.1016/j.jacc.2018.07.046
19. Hess CN, Huang Z, Patel MR, Baumgartner I, Berger JS, Blomster JI, Fowkes FGR, Held P, Jones WS, Katona B, et al. Acute limb ischemia in peripheral artery disease. *Circulation*. 2019;140:556–565. doi: 10.1161/CIRCULATIONAHA.119.039773
20. Xie JX, Glorioso TJ, Dattilo PB, Aggarwal V, Ho PM, Barón AE, Donaldson D, Armstrong EJ, Klein A, Giri J, et al. Effect of chronic kidney disease on mortality in patients who underwent lower extremity peripheral vascular intervention. *Am J Cardiol*. 2017;119:669–674. doi: 10.1016/j.amjcard.2016.10.053
21. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, Mills JL, Ricco J-B, Suresh KR, Murad MH, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *J Vasc Surg*. 2019;69:3S–125S.e40. doi: 10.1016/j.jvs.2019.02.016
22. Aboyans V, Ricco J-B, Bartelink M-L, Björck M, Brodmann M, Cohnert T, Collet J-P, Czerny M, De Carlo M, Debus S, et al. Editor's Choice - 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg*. 2018;55:305–368. doi: 10.1016/j.ejvs.2017.07.018
23. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FGR, Hamburg NM, Kinlay S, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:e686–e725. doi: 10.1161/CIR.0000000000000470
24. Arya S, Khakharia A, Binney ZO, DeMartino RR, Brewster LP, Goodney PP, Wilson PWF. Association of statin dose with amputation and survival in patients with peripheral artery disease. *Circulation*. 2018;137:1435–1446. doi: 10.1161/CIRCULATIONAHA.117.032361
25. Armstrong EJ, Chen DC, Singh GD, Amsterdam EA, Laird JR. Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use is associated with reduced major adverse cardiovascular events among patients with critical limb ischemia. *Vasc Med*. 2015;20:237–244. doi: 10.1177/1358863X15574321
26. Cho S, Lee Y-J, Ko Y-G, Kang TS, Lim S-H, Hong S-J, Ahn C-M, Kim J-S, Kim B-K, Choi D, et al. Optimal strategy for antiplatelet therapy after endovascular revascularization for lower extremity peripheral artery disease. *JACC Cardiovasc Interv*. 2019;12:2359–2370. doi: 10.1016/j.jcin.2019.08.006
27. Faglia E, Clerici G, Scatena A, Caminiti M, Curci V, Morabito A, Prisco V, Greco R, Edmonds M. Effectiveness of combined therapy with angiotensin-converting enzyme inhibitors and statins in reducing mortality in diabetic patients with critical limb ischemia: an observational study. *Diabetes Res Clin Pract*. 2014;103:292–297. doi: 10.1016/j.diabres.2013.12.060
28. Heart Protection Study Collaborative G. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. *J Vasc Surg*. 2007;45:645–654; discussion 653–644. doi: 10.1016/j.jvs.2006.12.054
29. Ostergren J, Sleight P, Dagenais G, Danisa K, Bosch J, Qilong Y, Yusuf S; investigators Hs. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. *Eur Heart J*. 2004;25:17–24. doi: 10.1016/j.ehj.2003.10.033
30. Tepe G, Bantleon R, Brechtel K, Schmehl J, Zeller T, Claussen CD, Strobl FF. Management of peripheral arterial interventions with mono or dual antiplatelet therapy–the MIRROR study: a randomised and double-blinded clinical trial. *Eur Radiol*. 2012;22:1998–2006. doi: 10.1007/s00330-012-2441-2

SUPPLEMENTAL MATERIAL

Table S1. Ipsilateral and contralateral contributions to major amputation.

	OVERALL - N=1,758 (%)	Discharge <10/1/2015 – N= 586 (%)	Discharge ≥10/1/2015 – N = 1,172 (%)
Major amputation - overall	224 (12.7)	76 (13.0)	148 (12.6)
Ipsilateral	N/A	N/A	122 (10.4)
Contralateral	N/A	N/A	33 (2.8)*

* Ipsilateral and contralateral amputations add to greater than overall major amputations because some patients had multiple amputations but only the first was considered in the MALE endpoint.

Table S2. Factors associated with MALE by one year among CLTI-PVI patients, excluding contralateral amputations.

	HR (95% CI)	p value
End stage renal disease on hemodialysis	1.64 (1.31 – 2.06)	<0.001
Prior MI	0.66 (0.50 – 0.88)	0.004
Superficial femoral artery treatment	1.53 (1.21 – 1.93)	<0.001
Bypass graft treatment	2.53 (1.28 – 4.98)	0.007
Procedural success	0.56 (0.42 – 0.77)	<0.001
Number of lesions treated	1.17 (1.05 – 1.29)	0.004

Table S3. Factors associated with mortality by one year among CLTI-PVI patients.

	HR (95% CI)	p value
Age	1.04 (1.03 – 1.06)	<.001
BMI	0.98 (0.96 – 1.00)	.013
ESRD on hemodialysis	2.27 (1.79– 2.88)	<.001
Severe lung disease	1.42 (1.12 – 1.80)	.004
Congestive heart failure	1.71 (1.41 – 2.08)	<.001
Prior CABG	1.35 (1.10 – 1.66)	.004
Family history of CAD	0.65 (0.44 – 0.94)	.023
Rutherford 4 PAD	0.75 (0.59 – 0.96)	.020
Antiplatelets at discharge	0.74 (0.58 – 0.95)	.016
Statins at discharge	0.73 (0.60 – 0.89)	.002