ORIGINAL RESEARCH

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

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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, profundap 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.
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
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 diagnost 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. 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
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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 1. Baseline Characteristics of Patients Receiving CLTI-PVI and Non-CLTI-PVI

|                         | Total, n (%) | CLTI, n (%) | Non-CLTI, n (%) |
|-------------------------|-------------|-------------|-----------------|
|                         | 3537        | 1758 (49.7%)| 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)     |

### Table 1. Continued

|                         | Total, n (%) | CLTI, n (%) | Non-CLTI, n (%) |
|-------------------------|-------------|-------------|-----------------|
| 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 (44.8)      |
| 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)        |
| Politeal                | 1007 (28.5) | 617 (35.1)  | 390 (21.9)      |
| Tibial                  | 1062 (30.0) | 866 (48.7)  | 206 (11.6)      |

(Continued)
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 lateraling 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 2. Medication Prescription at Discharge |
|---------------------------------------------|
| **Medication**                      | **CLTI, n (%)** | **Non-CLTI, n (%)** |
|----------------------------------------|----------------|---------------------|
| 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.

| Table 3. Thirty-Day and 1-Year Outcomes |
|----------------------------------------|
| **Non-CLTI PVI**                      | **CLTI PVI** |
|----------------------------------------|--------------|
| **30 d, n (%)**                        | **30 d, n (%)** | **1 y, 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 (6.5)    | 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.
Use of antiplatelet at discharge was 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 use at discharge were associated with lower likelihood of MACE.

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

| Factor                                      | 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 (0.52–0.98)     | 0.025   |
| Male sex                                    | 1.22 (1.02–1.47)     | 0.033   |
| Cerebrovascular disease                     | 1.23 (1.02–1.48)     | 0.026   |
| 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.

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

| Factor                                      | 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.
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.16,19

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.3,6,7,14,20 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

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**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.
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. 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.

**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**

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Supplemental Material
Tables S1–S3

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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.

| Factor                                         | 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.

| Factor                              | 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    |