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Major Adverse Limb Events and 1-Year Outcomes After Peripheral Artery Revascularization

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ABSTRACT

BACKGROUND Revascularization is important for symptom treatment and limb salvage in peripheral artery disease, yet little data exist on the incidence of post-procedure major adverse limb events (MALE) and longer-term outcomes.

OBJECTIVES This study sought to characterize hospitalizations and outpatient endovascular revascularizations after peripheral artery revascularization, assess temporal trends for outcomes, and identify factors associated with subsequent MALE hospitalization.

METHODS Patients undergoing peripheral artery revascularization between January 1, 2009, and September 30, 2014, in the Premier Healthcare Database were examined for the primary outcome of 1-year MALE hospitalization. Secondary outcomes included 1-year outpatient endovascular revascularization and limb-related, cardiovascular, and all-cause inpatient hospitalizations. Multivariable logistic regression was used to identify factors associated with 1-year MALE hospitalization.

RESULTS Among 381,415 revascularized patients, within 1 year post-index revascularization, 10.3% (n = 10,182) had a hospitalization for MALE, 11.0% (n = 42,056) had an outpatient endovascular revascularization, 18.8% (n = 71,663) had a limb-related hospitalization, 12.8% (n = 48,875) had a cardiovascular hospitalization, and 38.9% (n = 148,457) had any inpatient hospitalization. Over the study period, limb-related, cardiovascular, and all-cause hospitalizations decreased, whereas rates of outpatient endovascular revascularizations increased. Male sex, black race, Medicare and Medicaid insurance, diabetes, renal insufficiency, heart failure, smoking, baseline critical or acute limb ischemia, surgical revascularization, and noncardiology operator specialty were significantly associated with increased risk of MALE hospitalization.

CONCLUSIONS In contemporary practice, hospitalization for MALE occurs in 1 in 10 patients within 1 year after peripheral revascularization and is associated with patient and procedural factors. These data may inform efforts to improve post-procedure outcomes and limb-related clinical trial design. (J Am Coll Cardiol 2018;72:999–1011)

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ABBREVIATIONS AND ACRONYMS

ALI = acute limb ischemia

CI = confidence interval

CLI = critical limb ischemia

CPT = Current Procedural Terminology

HR = hazard ratio

ICD-9 = International Classification of Diseases-9th Revision

MALE = major adverse limb event(s)

MI = myocardial infarction

OR = odds ratio

PAD = peripheral artery disease

Peripheral artery disease (PAD) is a highly prevalent condition, affecting ~8.5 million Americans older than age 40 years and >200 million people worldwide (1,2). PAD is associated with significant limb-related morbidity and mortality, as well as decreased quality of life (2). Due to concomitant atherosclerotic disease in other vascular beds and medical comorbidities, patients with PAD are also at risk for cardiovascular events (3,4). Peripheral artery revascularization can help to improve symptoms and quality of life in PAD patients with claudication, while among patients with critical limb ischemia (CLI) and acute limb ischemia (ALI), goals of revascularization may include relief of ischemic pain, limb salvage, and improved wound healing.

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Despite potential benefits of peripheral revascularization, post-procedure risk for limb and cardiovascular events is elevated above that of patients with stable, unrevascularized PAD (5–7). In addition, rates of rehospitalization after vascular procedures have been high (8–10), and there has been a current focus by payers and hospital systems on reducing 30-day readmissions among high-risk populations (11). Recent studies have consequently examined readmissions among patients hospitalized for CLI, a high-risk subgroup with advanced PAD (12–14). Although these studies provide important insight into the burden of hospital readmissions among CLI patients, better understanding of subsequent inpatient and outpatient and longer-term outcomes for all PAD patients undergoing peripheral revascularization could help to optimize care for this broader population. Furthermore, there is growing interest in assessing limb-specific endpoints, particularly major adverse limb events (MALE), for PAD patients enrolled in cardiovascular outcomes clinical trials (4,6,15–17), yet little data on the incidence of MALE from contemporary, observational studies exist. Using a nationwide, all-comer health care database, we therefore sought to: 1) assess rates of subsequent inpatient hospitalization, focusing on admission for MALE, and outpatient endovascular peripheral procedures within 1 year after peripheral artery revascularization; 2) assess temporal trends for these outcomes; and 3) identify factors associated with 1-year MALE hospitalization.

METHODS

DATA SOURCE. Data for this study were from the Premier Healthcare Database, which at the time of analysis contained de-identified data from >687 million patient encounters, or approximately 1 in every 5 discharges in the United States. The Premier database contains data from standard hospital discharge files (e.g., demographic information and disease state); data from billed services, including medications, laboratory tests performed, and diagnostic and therapeutic services; and information on hospital characteristics. The Premier database provides a comprehensive view of inpatient and hospital-based outpatient visits from geographically diverse hospitals, and patient-related data are provided by the hospital for all payers and therapeutic areas. Patients can be tracked across all inpatient and hospital-based visits with a unique identifier within a single hospital system that shares the same billing infrastructure.

STUDY POPULATION. Patients ≥18 years of age with an inpatient or outpatient encounter with at least 1 International Classification of Diseases-9th Revision (ICD-9) discharge diagnosis code for PAD and at least 1 ICD-9 procedure code or Current Procedural Terminology (CPT) code for a peripheral endovascular or surgical revascularization procedure who were discharged between January 1, 2009, and September 30, 2014, were considered for inclusion in this study (Online Appendix). The time frame of the study was chosen to allow for 1 year follow-up for outcomes through September 30, 2015, while avoiding the transition from ICD-9 to ICD-10 codes. For patients with multiple peripheral revascularization encounters during the study period, the first qualifying procedure was considered the index encounter. Patients with missing age, sex, or death during the index encounter and those who were transferred to another acute-care facility or to hospice or who were treated at a hospital without any peripheral revascularization procedures within 1 year before the index encounter were excluded from the study sample.

OUTCOMES. The primary outcome of interest was inpatient hospitalization for MALE, defined as ALI (including thrombectomy and thrombolysis), major amputation (at or above the ankle), or surgical peripheral revascularization. Secondary outcomes of interest included outpatient endovascular peripheral revascularization, limb-related inpatient hospitalization, cardiovascular inpatient hospitalization, and all-cause inpatient hospitalization. Outcomes were

abstracted from the ICD-9 and CPT codes of each hospitalization (Online Appendix) and assessed at 30 days and 1 year after discharge from the index revascularization. Relevant ICD-9 and CPT codes were selected by consensus of the investigators and based on published data (12,13,18–22). Hospitalizations were categorized as limb-related, cardiovascular, or other. Limb-related hospitalizations included those for MALE, those involving an inpatient endovascular peripheral revascularization procedure, or those associated with a PAD diagnosis code in the primary position that otherwise did not qualify for MALE or involve an inpatient endovascular peripheral revascularization (termed other limb-related hospitalizations). Hospitalizations with a cardiovascular-related ICD-9 code in the primary position were classified as cardiovascular. Hospitalizations not qualifying for limb-related or cardiovascular causes were classified as other. Categories were not necessarily mutually exclusive, and encounters could be classified into multiple categories.

STATISTICAL ANALYSIS. Baseline variables were examined among the overall population and among patients with versus without 1-year hospitalization for MALE. Categorical variables were presented as number (percentage) and compared using chi-square tests, and continuous variables were presented as median (interquartile range) and compared using Mann-Whitney U tests. Outcomes of subsequent outpatient endovascular peripheral revascularizations and inpatient hospitalizations were assessed across the overall study period as well as within individual years to describe temporal trends.

Multivariable logistic regression was used to identify factors associated with hospitalization for MALE within 1 year after discharge from the index encounter. The following covariates, chosen based on clinical judgment and database availability, were included for adjustment: patient demographics (age, sex, race, payer type); comorbidities identified at admission or within 1 year before the index encounter (cerebrovascular disease, chronic pulmonary disease, renal insufficiency, prior stroke or transient ischemic attack, obesity, hypertension, diabetes, hyperlipidemia, heart failure, ischemic heart disease, atrial fibrillation or flutter, current or former smoker); visit characteristics (indication for revascularization; inpatient or outpatient status; endovascular, surgical, or hybrid revascularization; discharge status; procedure operator specialty); and hospital characteristics (rural or urban, teaching status, geographic region, bed size). Secondary models were also developed to identify factors associated with 1-year hospitalization for MALE among the subsets of patients with: 1) inpatient index encounters; and 2) outpatient index encounters. For the model with only inpatient index encounters, the following covariates were included for adjustment in addition to those listed previously: discharge medication (aspirin, $P2Y_{12}$ inhibitor, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, statin, nonstatin lipid-lowering therapy, beta-blocker, oral anticoagulant, cilostazol), hospital length of stay, and in-hospital events (myocardial infarction [MI], stroke, ALI, bleeding). Medication use during the last 2 days of inpatient encounters was used as a proxy for discharge medications, which were unavailable in the database. For all regression analyses, results were reported as odds ratio (OR) and 95% confidence interval (CI), and an alpha of <0.05 was considered statistically significant. Due to limited mortality data, which were only available for inpatient deaths occurring in a Premier hospital, censoring for death was not performed. All analyses were performed by Premier, Inc. using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. A total of 381,415 revascularized PAD patients were included in the final analysis population. Baseline patient, visit, and hospital characteristics are presented in Table 1. Overall, the median patient age was 69 years, 41.7% were women, and most patients were white and insured by Medicare. There was a significant burden of medical comorbidities in this population, including 71.0% with hypertension, 39.7% with diabetes, 53.4% with ischemic heart disease, 35.8% with current or former tobacco use, and 22.7% with renal insufficiency. Symptomatic PAD was the indication for revascularization for 70.7% of patients, with CLI and ALI accounting for 26.2% and 3.2% of procedures, respectively. Two-thirds of procedures were performed in the inpatient setting, and 77.3% of all procedures were performed via an endovascular only approach. Both inpatient and outpatient procedures were performed mainly by cardiology or vascular surgery specialists; slightly less than one-fifth of procedures were also performed by radiology and general surgery specialists. One-half of all index procedures were performed in the South, 90% were in urban institutions, and 47.8% were at teaching hospitals. Among inpatient index encounters, the median length of stay was 4 days, and 67.3% of patients

TABLE 1 Baseline Characteristics

	Overall Study Population (N = 381,415)	Without 1-Year Hospitalization for MALE (n = 342,094)	With 1-Year Hospitalization for MALE (n = 39,321)	p Value*	Standardized Difference†
Demographics					
Age, yrs	69 (61–77)	69 (61–77)	66 (58–75)	<0.0001	0.18
Age group				<0.0001	
18–64 yrs	137,046 (35.9)	120,109 (35.1)	16,937 (43.1)		0.16
65–74 yrs	122,832 (32.2)	110,626 (32.3)	12,206 (31.0)		0.03
>75 yrs	121,537 (31.9)	111,359 (32.6)	10,178 (25.9)		0.15
Female	159,193 (41.7)	143,714 (42.0)	15,479 (39.4)	<0.0001	0.05
Race				<0.0001	
White	278,084 (72.9)	251,526 (73.5)	26,558 (67.5)		0.13
Black	48,780 (12.8)	41,566 (12.2)	7,214 (18.3)		0.17
Other	54,551 (14.3)	49,002 (14.3)	5,549 (14.1)		0.01
Primary payer				<0.0001	
Commercial	71,521 (18.8)	64,349 (18.8)	7,172 (18.2)		0.02
Medicare	266,450 (69.9)	239,899 (70.1)	26,551 (67.5)		0.06
Medicaid	25,539 (6.4)	21,165 (6.2)	3,372 (8.6)		0.09
Other	18,905 (5.0)	16,681 (4.9)	2,224 (5.7)		0.04
Comorbidities					
Cerebrovascular disease	72,072 (18.9)	66,101 (19.3)	5,971 (15.2)	<0.0001	0.11
Chronic pulmonary disease	38,862 (10.2)	34,615 (10.1)	4,247 (10.8)	<0.0001	0.02
Renal insufficiency	86,398 (22.7)	75,166 (22.0)	11,232 (28.6)	<0.0001	0.15
Prior stroke/TIA	38,842 (10.2)	34,615 (10.1)	4,247 (10.8)	<0.0001	0.05
Obesity	45,783 (12.0)	40,772 (11.9)	5,011 (12.7)	<0.0001	0.02
Hypertension	270,649 (71.0)	241,059 (70.5)	29,590 (75.3)	<0.0001	0.11
Diabetes	151,534 (39.7)	132,411 (38.7)	19,123 (48.6)	<0.0001	0.20
Hyperlipidemia	210,625 (55.2)	189,344 (53.9)	19,251 (49.0)	<0.0001	0.02
Heart failure	77,555 (20.3)	68,490 (20.0)	9,065 (23.1)	<0.0001	0.08
Ischemic heart disease	203,737 (53.4)	184,486 (55.3)	21,281 (54.1)	<0.0001	0.10
Atrial fibrillation/flutter	50,668 (13.3)	45,201 (13.2)	5,467 (13.9)	0.0001	0.02
Current/former smoker	136,381 (35.8)	119,730 (35.0)	16,651 (42.3)	<0.0001	0.15
Visit characteristics					
Indication for revascularization				<0.0001	
Symptomatic PAD	269,535 (70.7)	250,575 (73.2)	18,960 (48.2)		0.53
CLI	99,761 (26.2)	81,004 (23.7)	18,757 (47.7)		0.52
ALI	12,119 (3.2)	10,515 (3.1)	1,604 (4.1)		0.05
Inpatient revascularization	254,385 (66.7)	225,565 (65.9)	28,820 (73.3)	<0.0001	0.16
Type of revascularization				<0.0001	
Endovascular	294,936 (77.3)	269,558 (78.8)	25,378 (64.5)		0.32
Surgical	45,079 (11.8)	38,012 (11.1)	7,067 (18.0)		0.20
Hybrid	41,400 (10.9)	34,524 (10.1)	6,876 (17.5)		0.22
Discharge status				<0.0001	
Home	330,085 (86.5)	298,491 (87.3)	31,594 (80.3)		0.19
Skilled nursing facility	37,525 (9.8)	31,832 (9.3)	5,693 (14.5)		0.16
Long-term or rehabilitation facility	13,805 (3.6)	11,771 (3.4)	2,034 (5.2)		0.08
Procedure operator specialty					
Inpatient index encounter				<0.0001	
Cardiology	82,840 (32.6)	78,204 (34.7)	4,636 (16.1)		0.44
Vascular surgery	84,601 (33.3)	71,905 (31.9)	12,696 (44.1)		0.25
General surgery	29,299 (11.5)	24,883 (11.0)	4,416 (15.3)		0.13
Radiology	13,318 (5.2)	11,364 (5.0)	1,954 (6.8)		0.08
Thoracic surgery	14,716 (5.8)	13,013 (5.8)	1,703 (5.9)		0.004
Other	29,611 (11.6)	26,198 (11.6)	3,415 (11.8)		0.01
Outpatient index encounter				<0.0001	
Cardiology	49,710 (39.1)	47,478 (40.7)	2,232 (21.3)		0.43
Vascular surgery	30,167 (23.7)	26,336 (22.6)	3,831 (36.5)		0.31
General surgery	8,820 (6.9)	7,701 (6.6)	1,119 (10.7)		0.15
Radiology	14,760 (11.6)	13,346 (11.5)	1,414 (13.5)		0.06
Thoracic surgery	3,428 (2.7)	3,043 (2.6)	385 (3.7)		0.06
Other	20,145 (15.9)	18,625 (16.0)	1,520 (14.5)		0.04

Continued on the next page

TABLE 1 Continued

	Overall Study Population (N = 381,415)	Without 1-Year Hospitalization for MALE (n = 342,094)	With 1-Year Hospitalization for MALE (n = 39,321)	p Value*	Standardized Difference†
Discharge medication‡					
Aspirin	171,258 (67.3)	153,957 (68.3)	17,301 (60.0)	<0.0001	0.17
$P2Y_{12}$ inhibitor	146,680 (57.7)	132,786 (58.9)	13,894 (48.2)	<0.0001	0.22
ACE inhibitor/ARB	120,986 (47.6)	107,815 (47.8)	13,171 (45.7)	<0.0001	0.04
Statin	156,869 (61.7)	140,726 (62.4)	16,143 (56.0)	<0.0001	0.13
Nonstatin lipid-lowering therapy	27,422 (10.8)	24,770 (11.0)	2,652 (9.2)	<0.0001	0.60
Beta-blocker	159,281 (62.6)	142,258 (63.1)	17,023 (59.1)	<0.0001	0.82
Oral anticoagulant	36,300 (14.3)	30,756 (13.6)	5,544 (19.2)	<0.0001	0.15
Cilostazol	8,483 (3.3)	7,333 (3.3)	1,520 (4.0)	<0.0001	0.04
Hospital length of stay, days‡	4 (2–8)	4 (2–8)	5 (3–10)	<0.0001	0.24
In-hospital events‡					
MI	4,675 (1.8)	4,232 (1.9)	443 (1.5)	<0.0001	0.03
Stroke	10,521 (4.1)	9,293 (4.1)	1,228 (4.3)	0.26	0.01
ALI	2,283 (0.9)	1,989 (0.9)	294 (1.0)	0.02	0.01
Bleeding	9,457 (3.7)	8,358 (3.7)	1,099 (3.8)	0.36	0.01
Hospital characteristics					
Urban	346,872 (90.9)	311,013 (90.9)	35,859 (91.2)	0.07	0.01
Teaching status	182,359 (47.8)	162,998 (47.6)	19,361 (49.2)	<0.0001	0.03
Geographic region				<0.0001	
Northeast	48,354 (12.7)	43,005 (12.6)	5,349 (13.6)		0.03
South	193,722 (50.8)	173,522 (50.7)	20,200 (51.4)		0.01
Midwest	81,734 (21.4)	73,948 (21.6)	7,786 (19.8)		0.04
West	57,605 (15.1)	51,619 (15.1)	5,986 (15.2)		0.003
Bed size				<0.0001	
<350 beds	130,011 (34.1)	117,217 (34.3)	12,794 (32.5)		0.04
350–549 beds	137,802 (36.1)	123,088 (36.0)	14,714 (37.4)		0.03
>550 beds	113,602 (29.8)	101,789 (29.8)	11,813 (30.0)		0.004

Values are median (interquartile range) or n (%). *Compares values for patients with vs. without 1-year major adverse limb event (MALE) hospitalization. †A standardized difference of >0.1 is considered clinically meaningful. ‡Among patients undergoing an inpatient index revascularization procedure.

ACE = angiotensin-converting enzyme; ALI = acute limb ischemia; ARB = angiotensin receptor blocker; CLI = critical limb ischemia; MI = myocardial infarction; PAD = peripheral artery disease; TIA = transient ischemic attack.

were discharged on aspirin, 57.7% on a $P2Y_{12}$ inhibitor, 14.3% on an oral anticoagulant, 61.7% on a statin, and 10.8% on a nonstatin lipid lowering therapy.

HOSPITALIZATION FOR MALE. Within 30 days after the index revascularization, 2.7% (n = 10,182) of patients were admitted for MALE (0.6%, n = 2,284 for ALI; 0.9%, n = 3,343 for major amputation; 1.4%, n = 5,459 for surgical revascularization). Within 1 year after the index revascularization, 10.3% (n = 39,321) of patients had a hospitalization for MALE (2.6%, n = 9,762 for ALI; 3.5%, n = 13,144 for major amputation; 6.0%, n = 22,994 for surgical revascularization). Compared with patients without 1-year MALE hospitalization, those with 1-year MALE hospitalization were younger, more often men and black, less likely to be insured by Medicare, more likely to be insured by Medicaid, and more likely to have a history of hypertension, diabetes, current or former smoking, and renal insufficiency. Patients with hospitalization for MALE within 1 year were also more likely to undergo the index revascularization for CLI or ALI, undergo surgical or hybrid procedures, and be discharged on oral anticoagulation, while they were less likely to be treated by cardiology specialists and discharged on antiplatelet therapy or statins.

After multivariable modeling, older age and female sex were associated with lower risk of 1-year MALE hospitalization, whereas black race; Medicaid and Medicare insurance; and comorbidities including prior stroke, diabetes, renal insufficiency, heart failure, and smoking were associated with higher risk of admission for MALE (C-statistic 0.70) (Table 2). Revascularization for CLI or ALI, undergoing surgical or hybrid revascularization, and having a procedure performed by a vascular or general surgeon or radiologist versus a cardiologist were significantly associated with increased risk of hospitalization for MALE within 1 year after the index encounter. Similar results were observed in

TABLE 2 Factors Associated With 1-Year Hospitalization for MALE

	OR (95% CI)	p Value
Demographics		
Age		
65–74 yrs vs. <65 yrs	0.82 (0.79–0.84)	<0.0001
≥75 yrs vs. <65 yrs	0.63 (0.61–0.65)	<0.0001
Female	0.91 (0.89–0.93)	<0.0001
Black vs. white race	1.27 (1.24–1.31)	<0.0001
Medicaid vs. commercial payer	1.14 (1.09–1.20)	<0.0001
Medicare vs. commercial payer	1.12 (1.08–1.16)	<0.0001
Comorbidities		
Cerebrovascular disease	0.80 (0.77–0.83)	<0.0001
Renal insufficiency	1.15 (1.12–1.18)	<0.0001
Prior stroke/TIA	1.15 (1.11–1.20)	<0.0001
Obesity	0.91 (0.88–0.94)	<0.0001
Diabetes	1.20 (1.17–1.23)	<0.0001
Hyperlipidemia	0.93 (0.91–0.96)	<0.0001
Heart failure	1.09 (1.06–1.12)	<0.0001
Ischemic heart disease	0.93 (0.90–0.95)	<0.0001
Current/former smoker	1.21 (1.18–1.24)	<0.0001
Visit characteristics		
Indication for revascularization		
ALI vs. symptomatic PAD	1.39 (1.31–1.47)	<0.0001
CLI vs. symptomatic PAD	2.24 (2.19–2.30)	<0.0001
Type of revascularization		
Surgical vs. endovascular	1.23 (1.19–1.27)	<0.0001
Hybrid vs. endovascular	1.39 (1.34–1.44)	<0.0001
Procedure operator specialty		
Vascular surgery vs. cardiology	2.13 (2.06–2.20)	<0.0001
General surgery vs. cardiology	2.09 (2.01–2.18)	<0.0001
Radiology vs. cardiology	2.11 (2.02–2.21)	<0.0001
Thoracic surgery vs. cardiology	1.86 (1.77–1.97)	<0.0001
Other vs. cardiology	1.58 (1.52–1.65)	<0.0001
Discharge to skilled nursing facility vs. home	1.10 (1.07–1.14)	<0.0001
Hospital characteristics		
Midwest vs. Northeast region	0.96 (0.92–0.998)	0.04
Bed size		
350–549 beds vs. <350 beds	1.14 (1.11–1.17)	<0.0001
>550 beds vs. <350 beds	1.05 (1.02–1.09)	0.002

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

models developed among patients with inpatient index encounters (Online Table 1) and those with outpatient index encounters (Online Table 2). In the inpatient model, discharge on oral anticoagulation was also associated with increased risk of 1-year MALE hospitalization.

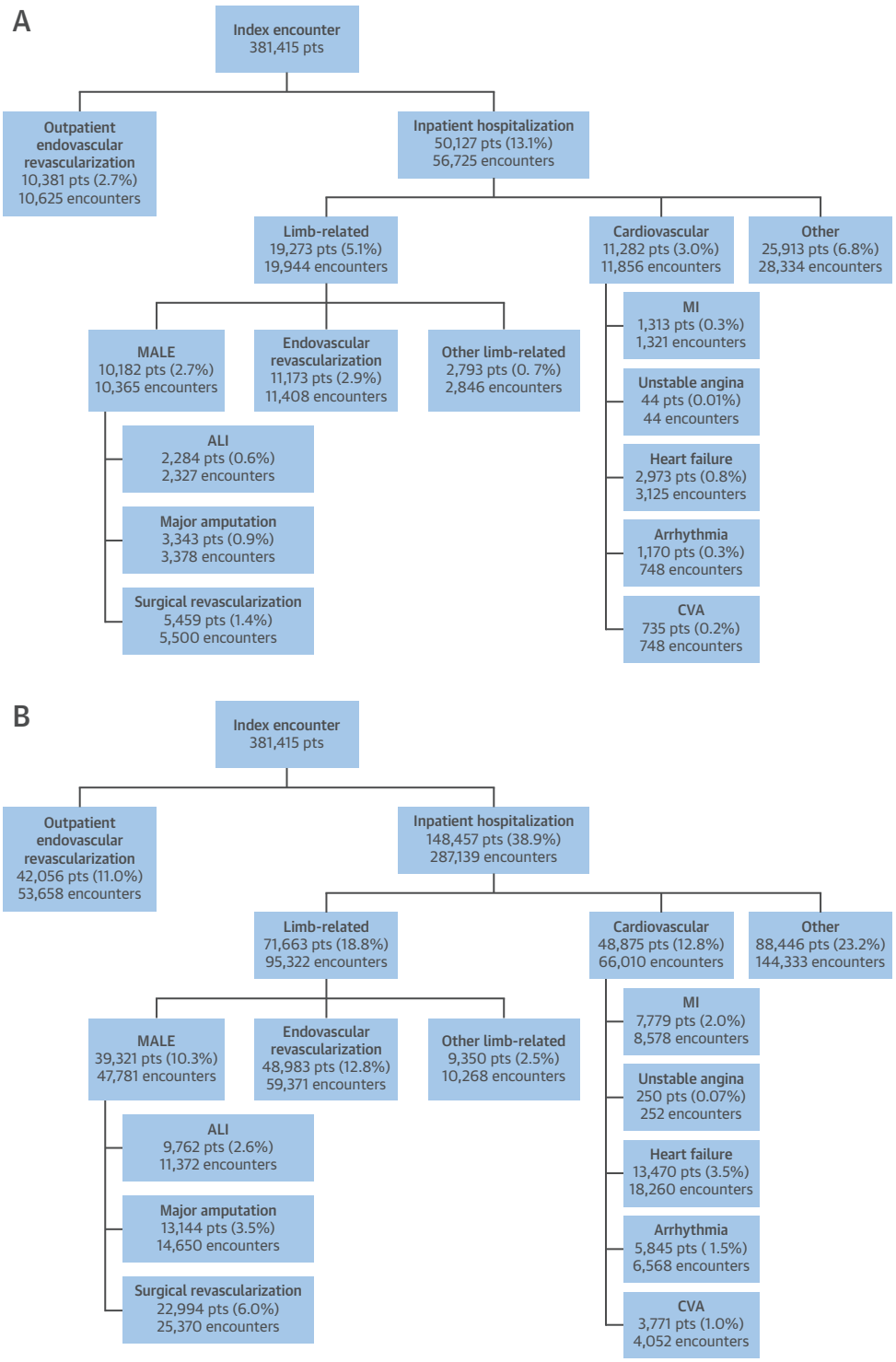
To explore the paradoxical age finding whereby older patients were at a lower risk of hospitalization for MALE within 1 year post-discharge, we compared baseline characteristics according to age (Online Table 3). We found that patients <65 years of age were more often black and insured by Medicaid. Despite being younger, one-third were insured by Medicare, and patients in this age group had a relatively high burden of comorbidities: 41.1% had diabetes, 67.0% had hypertension, 48.6% had ischemic heart disease, and 19.3% had renal insufficiency.

SECONDARY OUTCOMES. Within 30 days of discharge from the index encounter, 2.7% (n = 10,381) underwent at least 1 outpatient endovascular peripheral revascularization, and 13.1% (n = 50,127) had at least 1 inpatient hospitalization (Figure 1A). Overall, 5.1% (n = 19,273) of patients were admitted for limb-related causes, 3.0% (n = 11,282) for cardiovascular causes, and 6.8% (n = 25,913) for other reasons. Limb-related and cardiovascular admissions occurred in 38.4% and 22.5% of patients with at least one 30-day hospitalization. Hospitalization for MI, unstable angina, heart failure, arrhythmia, and stroke occurred in 0.3% (n = 1,313), 0.01% (n = 44), 0.8% (n = 2,973), 0.3% (n = 1,170), and 0.2% (n = 735), respectively, of the total study population.

Within 1 year of discharge from the index revascularization, 11.0% (n = 42,056) of the overall study population underwent at least 1 outpatient endovascular peripheral revascularization procedure, and 38.9% (n = 148,457) were hospitalized at least once (Figure 1B). Reasons for hospitalization were classified as limb-related, cardiovascular, and other for 18.8% (n = 71,663), 12.8% (n = 48,875), and 23.2% (n = 88,446) of all patients, respectively. Among patients with at least one 1-year hospitalization, 48.3% and 32.9% experienced respective limb-related and cardiovascular admissions. Overall, 12.8% (n = 48,983) of patients had an inpatient endovascular peripheral revascularization, and 2.5% (n = 9,350) of patients had other PAD limb-related hospitalizations not involving MALE or an endovascular revascularization. Within 1 year post-discharge from the index encounter, hospitalization for MI, unstable angina, heart failure, arrhythmia, and stroke occurred in 2.0% (n = 7,779), 0.07% (n = 250), 3.5% (n = 13,470), 1.5% (n = 5,845), and 1.0% (n = 3,771) of the study population.

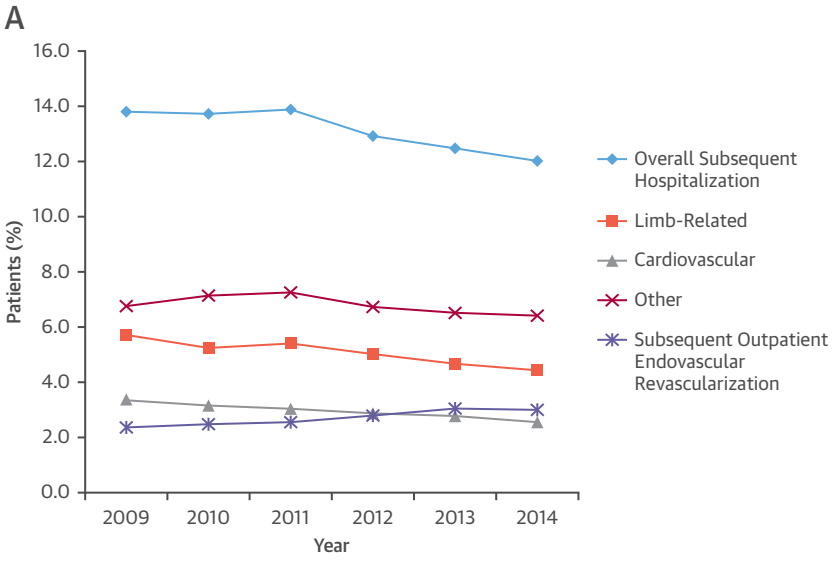
Temporal trends in 30-day and 1-year outcomes were examined. As shown in Figure 2A, overall subsequent hospitalizations within 30 days post-discharge from the index encounter trended down over time, with greater decreases in limb-related and cardiovascular hospitalizations than in hospitalizations for other causes. In contrast, subsequent 30-day outpatient endovascular peripheral revascularization procedures increased over the study period. Similar trends were seen for 1-year inpatient hospitalizations and 1-year outpatient endovascular peripheral revascularizations (Figure 2B).

FIGURE 1 **30-Day and 1-Year Outcomes After Peripheral Artery Revascularization**

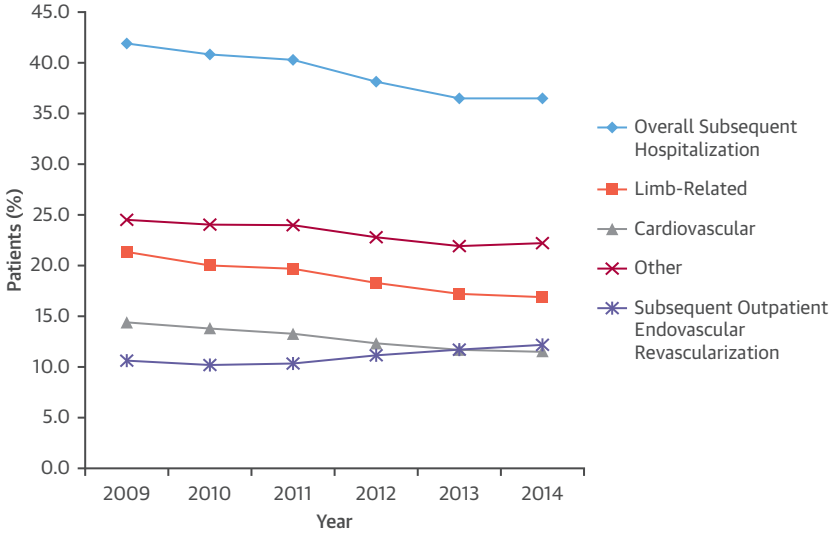


Flow diagrams depict the study patient population and outpatient endovascular peripheral revascularizations and inpatient hospitalizations within **(A)** 30 days and **(B)** 1 year post-discharge from the index encounter. Inpatient hospitalizations are classified according to limb-related, cardiovascular, or other causes for admission, and limb-related hospitalizations are further grouped into major adverse limb event (MALE), inpatient endovascular revascularization, or other limb-related categories. The components comprising MALE hospitalization are listed, and subtypes of cardiovascular hospitalizations are presented. Both patient-level and encounter-level data are provided but may not sum to 100%, as categories may not be mutually exclusive. ALI = acute limb ischemia; CVA = cerebrovascular accident; MI = myocardial infarction; pts = patients.

FIGURE 2 Temporal Trends in 30-Day and 1-Year Outcomes After Peripheral Artery Revascularization



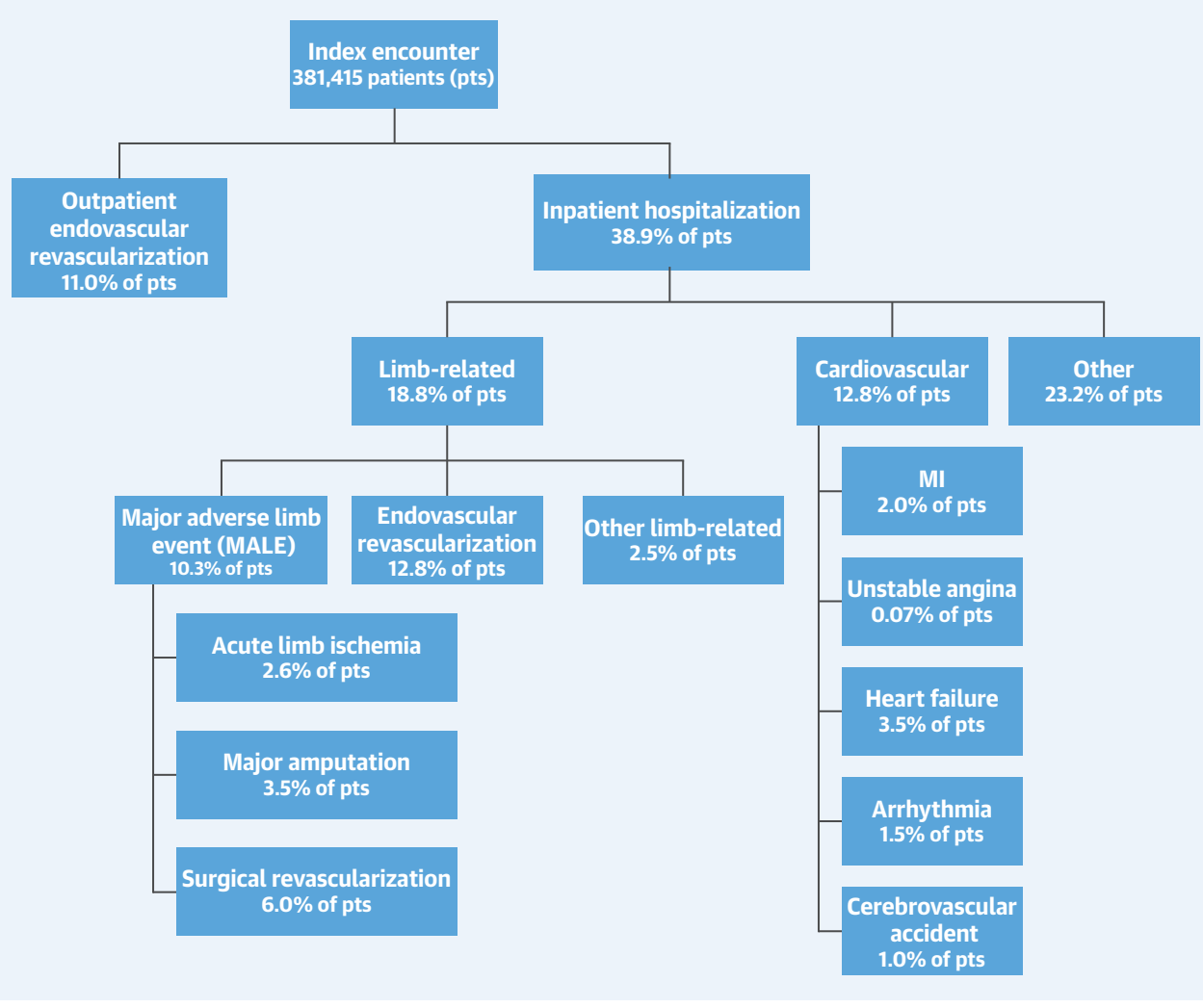
	2009	2010	2011	2012	2013	2014
Overall Subsequent Hospitalization, %	13.8	13.7	13.9	12.9	12.5	12.0
Limb-Related	5.7	5.2	5.4	5.0	4.7	4.4
Cardiovascular	3.4	3.2	3.0	2.9	2.8	2.6
Other	6.8	7.1	7.2	6.7	6.5	6.4
Outpatient Endovascular Revascularization, %	2.4	2.5	2.6	2.8	3.1	3.0



	2009	2010	2011	2012	2013	2014
Overall Subsequent Hospitalization, %	41.9	40.8	40.3	38.1	36.6	36.5
Limb-Related	21.4	20.0	19.7	18.3	17.2	16.8
Cardiovascular	14.4	13.9	13.3	12.3	11.7	11.6
Other	24.5	24.1	24.0	22.8	21.9	22.2
Outpatient Endovascular Revascularization, %	10.6	10.2	10.3	11.1	11.7	12.1

Shown are rates of overall, limb-related, cardiovascular, and other subsequent inpatient hospitalizations, as well as outpatient endovascular peripheral revascularization procedures within **(A)** 30 days and **(B)** 1 year after discharge from the index encounter for each year of the study period. Categories may not be mutually exclusive, and data from 2014 do not include the last quarter of the year.

CENTRAL ILLUSTRATION **1-Year Outcomes After Peripheral Artery Revascularization**



Hess, C.N. et al. J Am Coll Cardiol. 2018;72(9):999–1011.

Shown are outpatient endovascular peripheral revascularizations and inpatient hospitalizations within 1 year post-discharge from the index peripheral revascularization. Inpatient hospitalizations are classified according to limb-related, cardiovascular, or other causes for admission, and limb-related hospitalizations are further grouped into major adverse limb event (MALE), inpatient endovascular revascularization, or other limb-related categories. The components comprising MALE hospitalization are listed, and subtypes of cardiovascular hospitalizations are presented. Patient-level data are provided but may not sum to 100%, as categories may not be mutually exclusive. MI = myocardial infarction; pts = patients.

DISCUSSION

This large, observational study demonstrated that 1 in 10 PAD patients undergoing limb revascularization was hospitalized for MALE within the subsequent year. An additional 11% of patients underwent outpatient endovascular revascularization within that year, and 40% of patients had an all-cause inpatient hospitalization, of which one-half were limb-related and one-third were cardiovascular (Central Illustration). Over the study period, rates of all-cause, limb-related, and cardiovascular hospitalizations trended down, while use of subsequent outpatient endovascular revascularization procedures increased. We found that demographic factors, comorbid conditions, and procedural factors were significantly associated with 1-year hospitalization for MALE, which may help to identify high-risk patients.

Existing published reports regarding outcomes after peripheral artery revascularization is limited. Although prior studies have described cardiovascular and limb events after peripheral revascularization (5,20,23,24), these studies focused exclusively on 1 revascularization approach, used older data before improvements in medical therapy for PAD and the development of newer revascularization devices and strategies, only included inpatient populations, or were based outside of the United States, potentially limiting the generalizability of their results. Some of these studies also did not examine limb-related outcomes, whereas others restricted analyses to specific limb events, such as amputation or target lesion revascularization. Additionally, recent focus by payers and health care systems on reducing 30-day readmissions has prompted multiple efforts to characterize and understand readmissions among the PAD population (9,10,12–14,25). However, similar limitations exist for these studies, including restrictions in population to CLI patients, some of whom did not undergo revascularization; patients treated only as inpatients or in specific geographic regions; focus on surgical or endovascular revascularization; absent or limited assessments of limb-related outcomes; or small sample size.

Our study adds to current knowledge in the field. We used contemporary data from a nationwide, all-comer population with multiple payer representation and included a broad population of PAD patients. In general, rates of cardiovascular and limb events following peripheral revascularization are higher than for stable PAD patients (5–7), potentially related to procedural endothelial damage and inflammatory activation with subsequent risk for thrombosis and restenosis (26). Although CLI patients are a particularly high-risk PAD subgroup with end-stage disease associated with significant morbidity, mortality, and health care resource use, they make up the minority of PAD patients, accounting for 26.2% of our analysis population. Moreover, outpatient peripheral revascularization is common and represented one-third of our index encounters. Therefore, due to the overall increased risk of revascularized PAD patients and high volume of revascularization procedures performed for symptomatic PAD in inpatient and outpatient settings, our study population was intentionally broad.

Importantly, this study differs from prior analyses with regard to not only patient population but also outcomes examined. In addition to post-procedure inpatient hospitalizations, we included outpatient endovascular peripheral revascularizations to provide a more complete assessment of post-index procedure outcomes and burden of disease in this population. To that end, we categorized subsequent hospitalizations into cardiovascular, limb-related, and other reasons for admission and included analyses of temporal trends for these outcomes. Limb-related admissions were also further separated into MALE-related, inpatient endovascular revascularization, and other limb-related hospitalizations. The outcome of MALE has been variably defined to include components of ALI, thrombectomy, thrombolysis, major amputation, or major repeat revascularization (27,28). Recently, there has been growing interest in examining this endpoint or components thereof in cardiovascular clinical trials. In a comparison of ticagrelor plus aspirin versus aspirin alone in patients with prior MI, a subgroup analysis of patients with prior MI and PAD showed a significant reduction with ticagrelor in risk of MALE (hazard ratio [HR]: 0.65; 95% CI: 0.44 to 0.95) (15), while another trial found no benefit of ticagrelor over clopidogrel in preventing major cardiovascular events or ALI (HR: 1.02; 95% CI: 0.92 to 1.12) among patients with stable, symptomatic PAD (16). Treatment of patients with high-risk non–ST-segment elevation acute coronary syndromes with vorapaxar versus placebo showed statistically insignificant but numerically fewer peripheral revascularization procedures (8.1% vs. 9.0%; $p = 0.16$) and lower-extremity amputations (0.9% vs. 1.5%; $p = 0.11$) (29), whereas vorapaxar significantly reduced the rate of first ALI events compared with placebo among patients with stable atherosclerosis (HR: 0.58; 95% CI: 0.39 to 0.86) (6). Given these signals for benefit of antithrombotic therapies in reducing limb events and the fact that the PAD population has remained relatively understudied, additional trials examining MALE outcomes are to be expected and are currently enrolling (17). Observational studies such as ours, which assess MALE endpoints and components and are based in contemporary practice populations, may provide important data, such as event rates, that inform clinical trial design and help to address issues surrounding generalizability of clinical trial results.

Our study demonstrates that patients undergoing peripheral revascularization have significant residual risk of limb-related and cardiovascular hospitalizations, although our data suggest that there has been an overall decrease in subsequent inpatient hospitalizations. Although we also report that use of outpatient endovascular revascularization is increasing, consistent with prior findings (18), it is unlikely that the greater use of outpatient revascularization is numerically responsible for the observed decrease in post-procedure hospitalizations. With the

passage of the Affordable Care Act in 2010, national attention was focused on reducing readmissions among Medicare beneficiaries for 3 common conditions (MI, heart failure, and pneumonia), prompting numerous efforts aimed at reducing readmissions, albeit with variable success (30). Given that PAD is often considered a marker of systemic atherosclerosis and is commonly manifest in patients with coronary artery disease, some of these efforts directed primarily at heart failure and MI populations may have also resulted in reduced hospitalizations for PAD patients. Although the trend is encouraging, our data demonstrate that PAD patients undergoing revascularization, even for "low-risk" symptomatic PAD, still experience frequent limb-related and cardiovascular post-procedure hospitalizations, which may be preventable. Underuse of guideline-recommended therapies in PAD patients has been previously shown (31), which is consistent with our finding that only 61.7% of patients undergoing inpatient index revascularization were discharged on statin therapy. Whether improvements in medical therapy for PAD or other strategies, such as closer surveillance post-procedure, might help to reduce subsequent admissions requires further investigation.

To better understand patient outcomes after peripheral revascularization, we also assessed factors associated with 1-year hospitalization for MALE. As expected, revascularization for CLI or ALI increased subsequent risk of MALE hospitalization. Certain comorbid conditions, such as diabetes, renal insufficiency, heart failure, and smoking, have been previously identified as risk factors for unplanned readmission among CLI patients and were similarly associated with increased risk for MALE hospitalization in our study (13,25). These modifiable factors could be addressed by increasing provider and patient awareness of their prevalence in the PAD population and by improving treatment of each specific condition. Compared with commercial insurance, Medicaid and Medicare also increased risk for 1-year MALE hospitalization, which might be explained by lower socioeconomic status, unemployment, or lack of access to health care associated with the former and older age and more comorbidities associated with the latter. However, we noted that older age was significantly associated with lower risk for 1-year MALE admission. The data exploring this paradoxical finding demonstrate that younger patients in our study are a sick subgroup with an unexpectedly high proportion receiving Medicare benefits due to disability or need for dialysis and may help to explain the high risk of MALE hospitalization among these patients. These findings also highlight the large burden of comorbid diseases among PAD patients undergoing revascularization, regardless of age. Other potential explanations for the paradoxical association of older age with reduced risk for MALE hospitalization include greater use of lower-risk endovascular procedures (rather than amputation or surgical revascularization that would qualify for MALE) among older patients returning with limb-related events; greater number of comorbidities among older patients resulting in primary coding of a non-PAD-related diagnosis, even if the hospitalization was related to MALE; competing risk of death occurring at non-Premier hospitals among older patients; or confounding. Interestingly, a similar finding was observed though not further investigated in a recent analysis of readmissions among CLI patients (12): there was a significant interaction between age and insurance type, whereby Medicare patients <65 years of age had higher risk for 6-month unplanned readmission (OR: 1.64; 95% CI: 1.56 to 1.72) than patients 65 to 80 years of age (OR: 1.31; 95% CI: 1.26 to 1.35) or patients >80 years of age (OR: 1.21; 95% CI: 1.16 to 1.25).

Finally, we also observed a significant increase in risk of 1-year MALE hospitalization for patients undergoing procedures performed by vascular or general surgery operators. In conjunction with our finding that a surgical or hybrid index procedure was a risk factor for 1-year MALE hospitalization, this may partially reflect the greater baseline risk of patients undergoing higher risk surgical revascularization procedures. However, acute bypass graft thrombosis is a frequent cause of ALI (6), and this may represent a modifiable risk factor for MALE, for example, through improvements in surgical technique or adjuvant antithrombotic therapy. In addition, having a procedure performed by a noncardiology, nonsurgical specialty operator was also associated with increased MALE risk. Although this finding could be related to previously described differences among operator specialties in the management of PAD patients after revascularization (19), it also suggests that procedures should be performed by higher-volume specialists, as relationships between operator volume and outcomes have been previously demonstrated for other procedures (32). Given the complexity of PAD patients overall and risk for cardiovascular as well as limb-related events post-procedure, a multidisciplinary approach to patient care, including input from a cardiovascular specialist, may help to improve outcomes in this population.

STUDY LIMITATIONS. First, this analysis was retrospective and observational. Despite multivariable

adjustment, unmeasured confounding may remain. Second, data were administrative and subject to errors in coding and potential misattribution. Third, we did not have clinical variables, including those related to severity of disease, or laboratory values, and medication billing data from the last 2 days of hospitalization was used as a proxy for discharge medication and were only available for inpatient index encounters. Fourth, hospitals are not required to submit all CPT codes to Premier, and some CPT-based procedures may be under-reported. Fifth, hospital contributions of data to the Premier Healthcare Database are voluntary, and the study cohort may not be truly representative of the overall patient population undergoing peripheral revascularization, limiting the generalizability of our results. Finally, subsequent outpatient endovascular revascularization procedures and hospitalizations occurring at non-Premier hospitals could not be identified, nor could we identify patients who died outside of a Premier hospital to account for the competing risk of death.

CONCLUSIONS

In this study of 381,415 patients undergoing peripheral artery revascularization, subsequent hospitalizations and outpatient endovascular revascularization procedures were common. Within 1 year after the index revascularization, a significant proportion of patients were hospitalized for limb-related and cardiovascular causes, with 1 in 10 patients admitted for MALE. Although overall subsequent hospitalizations trended down during the study period, the residual risk for post-procedure limb-related and cardiovascular events remains high. We identified multiple demographic, patient, and procedural factors associated with risk of 1-year hospitalization for MALE. Based on these findings, efforts to reduce the burden of comorbidities, improve surgical revascularization techniques or concomitant antithrombotic therapies, and implement a multidisciplinary approach to the care of PAD patients may represent actionable strategies to reduce hospitalization for MALE.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with PAD, additional endovascular procedures and hospitalization for MALE are common within 30 days and 1 year after revascularization. Risk factors for MALE include male sex, black race, insurance under Medicaid or Medicare, diabetes, renal insufficiency, heart failure, smoking, initial intervention for CLI or ALI, surgical revascularization, and certain operator characteristics.

TRANSLATIONAL OUTLOOK: Strategies that address these risk factors, including better management of comorbidities and multidisciplinary team-based care, should be evaluated to improve the outcomes of peripheral artery revascularization.

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KEY WORDS outcomes, peripheral artery disease, revascularization

APPENDIX For supplemental tables, please see the online version of this paper.