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ORIGINAL RESEARCH

Long-Term Outcomes of Peripheral Artery Disease in Veterans: Analysis of the Peripheral Artery Disease Long-Term Survival Study (PEARLS)

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BACKGROUND: Contemporary research in peripheral artery disease (PAD) remains limited due to lack of a national registry and low accuracy of diagnosis codes to identify patients with PAD.

METHODS: Leveraging a novel natural language processing system that identifies PAD with high accuracy using ankle-brachial index and toe-brachial index values, we created a registry of 103 748 patients with new-onset PAD in the Veterans Health Administration. Study end points include mortality, cardiovascular events (hospitalization for acute myocardial infarction or stroke) and limb events (hospitalization for critical limb ischemia or major amputation) and were identified using Veterans Affairs and non–Veterans Affairs encounters.

RESULTS: The mean age was 70.6 years; 97.3% were male, and 18.5% self-identified as Black. The mean ankle-brachial index value was 0.78 (SD: 0.26) and the mean toe-brachial index value was 0.51 (SD: 0.19). A majority of patients were current (27.1%) or former (30.0%) smokers. Prevalence of hypertension (86.6%), heart failure (22.7%), diabetes (54.8%), chronic kidney disease (23.6%), and chronic obstructive pulmonary disease (35.4%) was high. At 1 year, 9.4% of patients had died. The 1-year incidence of cardiovascular events was 5.6 per 100 patient-years and limb events was 7.0 per 100 patient-years.

CONCLUSIONS: We have successfully launched a registry of >100 000 patients with a new diagnosis of PAD in the Veterans Health Administration, the largest integrated health system in the United States. The incidence of death and clinical events in our cohort is high. Ongoing studies will yield important insights regarding improving care and outcomes in this high-risk group.

Key Words: natural language processing ■ peripheral artery disease ■ survival ■ veterans

An estimated 8 to 12 million Americans experience lower extremity peripheral artery disease (PAD).[1,2] Although PAD shares risk factors (eg, diabetes, smoking, and hypertension) with other atherosclerotic vascular diseases such as coronary artery disease, patients with PAD experience a higher rate of cardiovascular (myocardial infarction, stroke) and limb events (critical limb ischemia [CLI], amputation), which

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CLINICAL PERSPECTIVE

What Is New?

- Using a validated natural language processing system that can extract ankle-brachial index and toe-brachial index values from ankle-brachial index reports, we have launched the PEARLS (Peripheral Artery Disease: Long Term Survival Study), a registry of >100 000 Veterans with new-onset peripheral artery disease.
- Overall burden of risk factors and comorbidities (smoking, diabetes, hypertension, hyperlipidemia, and co-existing atherosclerotic cardiovascular disease) was high.
- Within 1 year, nearly 10% of patients had died, and the overall incidence of cardiovascular and limb events was high, underscoring the importance of developing strategies for risk reduction.

What Are the Clinical Implications?

- The PEARLS study represents a novel approach to developing large-scale electronic health record–based registries. Ongoing studies will yield important insights regarding improving care and outcomes in this high-risk group.

Nonstandard Abbreviations and Acronyms

CDW	corporate data warehouse
PEARLS	peripheral artery disease: long-term survival
TBI	toe-brachial index
VA	Veterans Affairs
VHA	Veterans Health Administration

contribute to excess disability, death, and medical expenditures.[3–6] Importantly, racial and ethnic disparities in the incidence and outcomes of PAD have been reported, with a higher incidence of lower extremity amputations in Black, as compared with White, individuals with PAD.[7,8]

While clinical practice guidelines recommend a multipronged strategy including medications (eg, statins), risk factor control (blood pressure and diabetes), lifestyle changes, and revascularization in select patients,[9] the above therapies are unevenly applied in clinical practice.[10–16] This may be due to a paucity of contemporary evidence regarding existing treatments on long-term outcomes. Unlike coronary artery disease, there are also unique challenges to reliably identifying patients with PAD within electronic health records (EHR) data; existing PAD diagnosis codes historically have had low positive predictive values ranging from 27.5% to 69.4%.[17–20] The limited accuracy of diagnosis codes has hampered the development of large registries to improve care and outcomes in PAD.

We recently developed and validated a natural language processing (NLP) system that can extract ankle-brachial index (ABI) and toe-brachial index (TBI) values from ABI test report documents in the Veterans Affairs (VA) EHR and use these direct measures of ABI and TBI values to identify patients with PAD.[21] In contrast to using only *International Classification of Diseases* (*ICD*) codes, our NLP-based approach had a sensitivity of 83.1%, specificity of 93.1%, and positive predictive value of 92.3% for identifying PAD.[21] Leveraging this NLP system, we have launched the PEARLS (Peripheral Artery Long-term Survival Study), a longitudinal study of PAD in the Veterans Health Administration (VHA), the largest integrated health system in the United States. In this article, we describe the creation of the PEARLS registry, a contemporary cohort of newly diagnosed patients with PAD identified using our novel NLP system in the VHA EHR. We also provide descriptive data on the baseline characteristics of our cohort including data on demographics, comorbidities, medications, and longitudinal data on 1-year incidence of mortality, and cardiovascular and limb events.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject protocols may be sent to Veterans Affairs Informatics and Computing Infrastructure (VINCI) at vinci@va.gov. The study adhered to the Strengthening and Reporting of Observational Studies in Epidemiology reporting guidelines for observational studies and was approved by the Institutional Review Board and Research & Development Committees at Dallas, Iowa City, and Tennessee Valley Health System VA centers as well as University of Texas Southwestern Medical Center and University of Iowa, who waived the need for informed consent.

The primary objective of the study was to develop a longitudinal cohort of patients with incident PAD using our novel NLP system. In the first stage of cohort creation, we executed the NLP system on the entire corpus of ABI report documents in the VA's EHR. Among patients identified as having PAD, we applied additional criteria to restrict our cohort to patients with a new diagnosis of PAD and those who use VA regularly for health care (Figure 1). Next, we identified

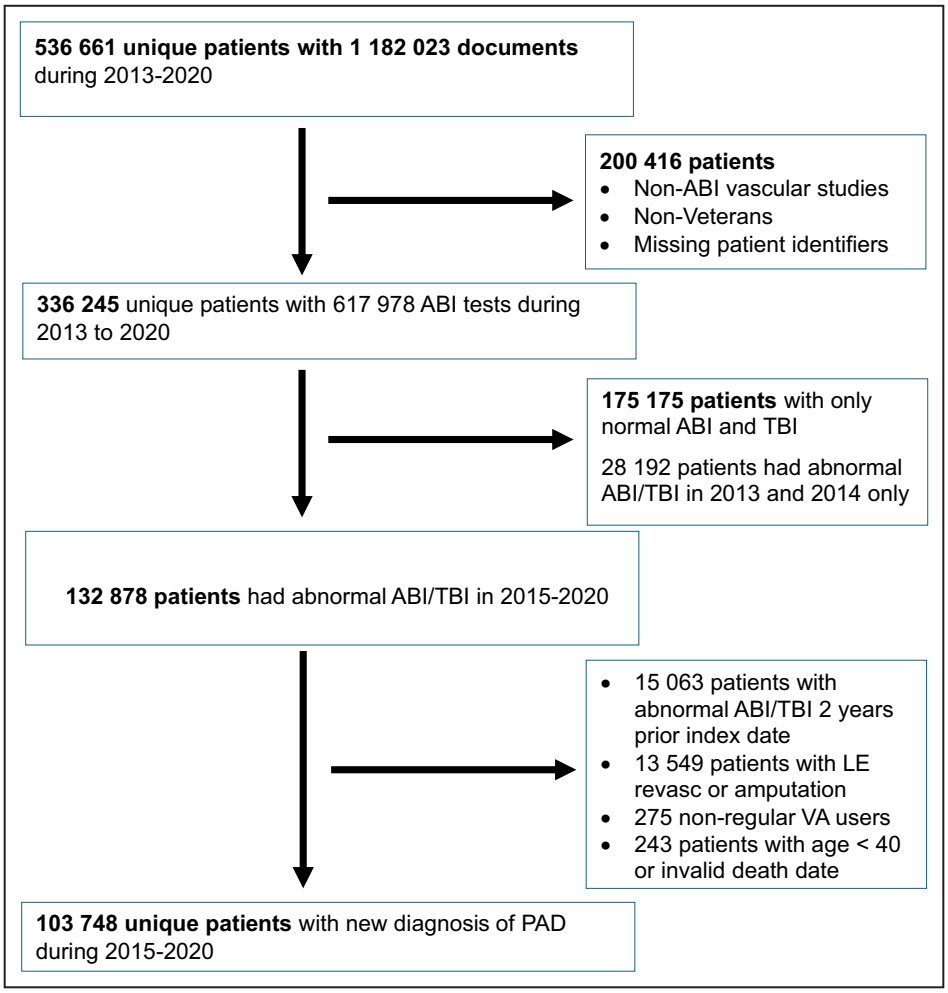

Figure 1. Study flowchart.
ABI indicates ankle-brachial index; LE, lower extremeity; PAD, peripheral artery disease; TBI, toe-brachial index; and VA, Veterans Affairs.

baseline demographics, comorbidities, smoking status, medications, vital signs, and laboratory values for our cohort. We followed the cohort longitudinally for clinical events using a combination of VA and non-VA (Medicare) data sources to ensure complete follow-up.

Data Sources

The list of data sources used in the current study is summarized in Table S1. The VA Corporate Data Warehouse (CDW) is a national repository of clinical data for patients receiving care at a VA facility. Because the VA is a single-payer health care system, it generates data from clinical functions (eg, clinical notes, procedural and radiology reports) and claims-based functions (eg, clinical diagnoses and procedures using *International Classification of Diseases Ninth and Tenth Clinical Modification* (*ICD-9 CM* and *ICD-10 CM*) and Current Procedural Terminology codes). The above data are available for inpatient and outpatient encounters. In addition, data on smoking status, vital signs from each clinical encounter, laboratory test results, and prescriptions filled at a VA pharmacy are also available. Table S1 includes details of data domains within the CDW that were used for identifying study variables. Unique patient identifiers allow linkage of data across domains to create a comprehensive patient record.

Since Veterans may also receive care at a non-VA facility, relying on VA data alone may not provide complete information regarding clinical events after PAD diagnosis. Therefore, we obtained 2 additional sources of data to supplement clinical data available in the VHA. These include the (1) Fee-basis files and Consolidated Dataset (CDS) files and (2) Medicare claims. The Fee-basis (2019 and earlier) and Consolidated Dataset (2020 onwards) data include claims arising from services provided to Veterans at a non-VA facility (or by a non-VA provider) that are paid by the VA. Typically, the VA pays for emergent

care received by a Veteran at a non-VA facility (eg, hospitalization for acute myocardial infarction [MI] or stroke). The VA also pays for routine visits at a non-VA facility if traveling to a VA facility for the same services imposes undue burden (eg, vascular surgery clinic at a non-VA facility near a Veteran's home if comparable services at a VA facility require long travel). Each year the Veterans Affairs Information Resource Center obtains 100% Medicare enrollment and claims data from the Center for Medicare and Medicaid for all Veterans regardless of whether they receive care at the VA or not. These include Part A (fee for service), Part B & Carrier (outpatient), Part C (Advantage), and Part D (medications). For our cohort, Veterans Affairs Information Resource Center provided all Part A, Part B, Part C, and Part D claims for Veterans in our cohort from 2015 to 2022 (Part C data were only available through 2021). Because >70% of Veterans in our cohort were older than 65 years of age (Medicare eligible) at the time of PAD diagnosis, the addition of Medicare claims ensured more comprehensive follow-up from clinical encounters outside the VA, especially those older than 65 years of age. Thus, the availability of these additional data sources ensures near complete follow-up of our cohort of patients with PAD.

ABI Reports

Within the CDW data, we identified all reports of ABI tests performed during 2013–2020 at a VA facility. Depending on the facility, ABI tests may be performed in vascular surgery, radiology, or primary care. Therefore, ABI report documents can be found in either the Text Integration Utility or Radiology domain within Unstructured Clinical data in CDW. In both domains, documents are organized into document types, with each document type having a unique ID and an associated title (eg, "Vascular Lab ABI report"). The document type IDs are unique to each VA facility and can be used to identify all individual documents within that facility (eg, all ABI test results that are reported using the "Vascular Lab ABI report" title would have a common document type ID). Often, a facility uses more than 1 document type for reporting ABI results, especially if ABI tests are performed by multiple specialties at that facility. We included all possible document type IDs used for reporting ABI results at each facility. Finally, in some instances, a facility used a "generic" document type ID (eg,"Vascular Lab Report") for reporting both ABI studies and non-ABI vascular studies (eg, carotid duplex, etc.). Such generic document type IDs were also included. In our validation study, the NLP system extracted no false positive ABI or TBI values from non-ABI vascular studies.[21] A total of 424 document type IDs used for reporting ABI results in the VHA during 2013–2020 were identified, which corresponded to 1 182 023 individual documents.

NLP System for PAD Identification

The development and validation of the NLP system has been previously reported.[21] Briefly, the NLP system uses regular expressions to label phrases commonly associated with the concept of ABI or TBI, their values, and laterality and uses a machine learning approach (random forests) for identification of these concepts. Through a process of iterative learning, cross-validation-based evaluation, error analysis, and modification to improve performance on a total of 600 ABI report documents, the NLP system was tested in a final set of 200 documents, where it achieved an overall precision of 0.85, recall of 0.93, and F1-measure of 0.89. Next, we evaluated an algorithm (Figure S1) that classified patients as PAD if they had an NLP-extracted ABI of ≤0.9 or a TBI ≤0.7 in any limb.

NLP Deployment

Since the NLP system was developed using only a small random sample of individual ABI documents (800 total), certain adaptations were necessary to handle the large document corpus for implementation in the entire VHA without losing accuracy. In our development work, we used the same text-based features for random forest model training and subsequent testing. However, this approach proved to be infeasible at scale due to temporal and spatial requirements, which requires re-training the random forest model for every document. To overcome this challenge, we first redesigned and refactored the code underlying the tool and re-tested model performance using the previous training and test corpora to ensure no change in performance. We also built a disk-based storage system that could hold millions of files and allow for rapid retrieval of documents without consuming excessive disk space. Finally, we created a database programming script that can identify PAD based on extracted ABI and TBI values (Figure S1). With these changes, we were able to process all of the documents in a total of 95 hours. This equated to 3.48 documents processed per second or >300 000 documents per day.

Creation of the PEARLS Cohort

Since our overall objective was to identify Veterans with a new diagnosis of PAD during 2015–2020, we intentionally added 2 additional years of ABI data (2013–2014) as a "look-back" period. This was done to ensure that patients identified as PAD based on abnormal ABI or TBI for the first time in 2015–2020 did not also have abnormal ABI or TBI value during the prior 2 years.

Figure 1 shows the derivation of our study cohort. After processing ≈1.2 million documents and excluding non-ABI vascular studies, non-Veterans, and patients missing unique IDs, a total of 336 245 patients with 617 978 ABI report documents remained. Among these patients, 132 878 (39.5%) had at least 1 ABI report meeting criteria for PAD (ie, ABI value of ≤0.9 or a TBI value ≤0.7, Figure S1) during 2015–2020. For each patient, all ABI reports were arranged in chronological order, and the index date (date of PAD diagnosis) was defined as the earliest date of abnormal ABI or TBI value in any limb during 2015–2020. From this sample, we excluded patients with evidence of PAD during 2013 and 2014 (2-year look-back) or a previous history of lower extremity revascularization or amputation in the 2 years before the index date. Additional exclusions were nonregular users of VA services (<2 outpatient, or 1 inpatient and 1 outpatient visit in the prior 2 years), age <40 years on index date (because PAD is rare in those younger than 40 years), and death before the index date (data coding errors). Our final sample included 103 748 patients with a new diagnosis of PAD during 2015–2020.

Study Outcomes

The registry collected a number of outcomes relevant to PAD. All-cause mortality was determined using the VA Death Ascertainment file. Other important outcomes that were collected included cardiovascular events (hospitalization for acute MI or ischemic stroke) and limb events (CLI and major amputation). Major amputation was defined as any amputation above the ankle joint. The diagnosis and procedure codes used to identify these events are listed in Table S2. Hospitalization for MI, stroke, and CLI were included only when they were reported as primary diagnosis on the inpatient encounter because multiple prior studies have demonstrated better accuracy only when the primary diagnosis is considered.[22–26]

Study Variables

Demographic characteristics included age, sex, and race (White, Black, other), and ethnicity (Hispanic versus non-Hispanic). Smoking status up to 12 months before the index date was determined using the health factors table in VHA CDW, which contains details on routine screenings and social factors that impact health. Comorbidities were based on clinical diagnosis entered in inpatient and outpatient encounters from the VA, Fee-basis and Consolidated Dataset files during the 2 years before the index date, and defined using algorithms originally developed by Elixhauser, and updated by Quan.[27] We used vital signs data from outpatient encounters to determine baseline systolic and diastolic blood pressure during 24 months before the index date. We used laboratory data to determine baseline levels of total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, and hemoglobin A1c levels within 12 months before the index date. Severity of PAD was categorized based on the lowest NLP-extracted ABI or TBI value from the qualifying ABI report as follows: mild: 0.8≤ABI≤0.9 or 0.6≤TBI≤0.7; moderate: 0.5≤ABI<0.8 or 0.4≤TBI<0.6; severe: 0≤ABI<0.5 or 0≤TBI<0.4. Smoking status was determined using Health Factor data available in Veterans Affairs Informatics and Computing Infrastructure and reported as current smoker, former smoker, nonsmoker, and unknown. We identified prescription fills using VA Pharmacy and Medicare Part D data to determine baseline use of lipid-lowering drugs, antiplatelet drugs, anticoagulants, and antihypertensive and antidiabetic drugs. High-intensity statin was defined as simvastatin ≥80 mg, atorvastatin ≥40 mg, or rosuvastatin ≥20 mg. For each drug, we defined active use at baseline as filling a prescription for that drug before the index date within a time period that was less than or equal to twice the days' supply dispensed. For example, a patient with PAD with an index date of August 1, 2015, who filled a 30-day supply of atorvastatin on June 15, 2015 (46 days before the index date) would be considered an active statin user because the drug was filled within 60 days (2×30 days' supply).

Statistical Analysis

Baseline characteristics of our study cohort were reported using means (SDs) and frequencies (proportions) as appropriate. Next, we examined the overall rate of each study end point: mortality, hospitalization for MI or stroke (cardiovascular events), and CLI and amputation (limb events) at 1-year follow-up. We also constructed survival curves as well as the cumulative index function for the study end points over a 1-year follow-up period. For nonfatal end points, the incidence rates were computed after accounting for the competing risk of death and expressed as per 100 patient-years. Next, we constructed Cox proportional hazards models to evaluate patient variables associated with 1-year mortality. Patient demographics (age, sex, race, and ethnicity), severity of PAD, smoking, and comorbidities were included as fixed effects to evaluate their independent association with 1-year mortality. Finally, we also examined the proportion of events that were identified using different data sources (VA data, Fee-basis, Medicare fee-for-service, and Medicare Advantage) to quantify the incremental contribution of nontraditional sources of data for evaluating clinical outcomes in our cohort. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Table 1. Baseline Characteristics of Veterans With New Diagnosis of Peripheral Artery Disease 2015 to 2020

Variable	n=103 748
Demographics	
Mean age, y ±SD	70.6±9.1
Male sex	100 972 (97.3%)
Race	
White	77 321 (74.5%)
Black	19 208 (18.5%)
Other[§]	1660 (1.6%)
American_indian	686 (0.7%)
Asian	339 (0.3%)
Native_hawaiin	635 (0.6%)
Unknown	4836 (4.7%)
Ethnicity	
Hispanic	3130 (3.0%)
Not Hispanic	96 951 (93.4%)
Smoking status	
Current	28 086 (27.1%)
Former	31 132 (30.0%)
Nonsmoker	13 160 (12.7%)
Unknown	31 370 (30.2%)
PAD severity[‡]	
Mild	30 337 (29.2%)
Moderate	49 877 (48.1%)
Severe	23 534 (22.7%)
Comorbidities[†]	
Hypertension	89 827 (86.6%)
Diabetes	56 904 (54.8%)
Chronic kidney disease	24 467 (23.6%)
Chronic obstructive pulmonary disease	36 676 (35.4%)
Arrhythmia	31 390 (30.3%)
Heart failure	23 548 (22.7%)
Coronary artery disease	44 462 (42.9%)
Prior history of MI	11 252 (10.8%)
Cerebrovascular disease	24 731 (23.8%)
Cancer	16 285 (15.7%)
Dementia	5232 (5.0%)
Depression	31 750 (30.6%)
Chronic liver disease	9699 (9.3%)
Obesity	25 244 (24.3%)
Anemia	11 401 (11.0%)
Valvular heart disease	11 010 (10.6%)
Weight loss	7814 (7.5%)
Blood pressure, mean ±SD*	
Systolic	133±19
Diastolic	73±11
Laboratory values, mean ±SD*	
Total cholesterol	162 mg/dL ±44.6
LDL-cholesterol	91.0 mg/dL ±37.2
HDL-cholesterol	43.1 mg/dL ±14.1
Triglycerides	157.1 mg/dL ±123.6
Hemoglobin A1c	6.9% ±1.6
ABI and TBI values, mean ±SD*	
ABI in worst limb	0.78±0.26
TBI in worst limb	0.51±0.19

Data in the table represent N (%), unless otherwise specified. ABI indicates ankle-brachial index; MI, myocardial infarction; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAD, peripheral artery disease; and TBI, toe-brachial index.

*Data on vital signs were available in 98 869 (95.3%) patients, total cholesterol: 89 818 (86.6%) patients, LDL-cholesterol: 89 117 (85.9%) patients, HDL-cholesterol: 89 569 (86.3%) patients, triglycerides: 88 905 (85.6%) patients, hemoglobin A1c: 79 918 (77.0%) patients, ABI values: 99 266 (95.7%) patients, and TBI values: 57 010 (54.5%) patients.

[†]All comorbidities were defined using *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *ICD-10* diagnosis and procedure codes based on the algorithms developed by Elixhauser and updated by Quan.[27]

[‡]PAD severity was defined using the lowest ABI and TBI value as follows: Mild: 0.8≤ABI≤0.9 or 0.6≤TBI≤0.7; Moderate: 0.5≤ABI<0.8 or 0.4≤TBI<0.6; severe: 0≤ABI<0.5 or 0≤TBI<0.4.

[§]Other includes American Indian 686 (0.7%); Asian 339 (0.3%); Native Hawaiian 635 (0.6%).

RESULTS

Table 1 shows baseline characteristics of our cohort. Among 103 748 eligible patients with PAD, the mean age was 70.6 years (SD of 9.1 years), and the majority (97.3%) were men. Nearly 1 in 5 patients (18.5%, n=19 208) were of Black race and 3.0% (n=3130) were of Hispanic ethnicity. The mean (SD) ABI and TBI in the worst limb was 0.78 (0.26) and 0.51 (0.19), respectively. Overall, 27.1% of our cohort were currently smoking and 30.0% were former smokers. Overall, there was a high prevalence of hypertension (86.6%), coronary artery disease (42.9%), cerebrovascular disease (23.8%), diabetes (54.8%), chronic kidney disease (23.6%), and chronic obstructive pulmonary disease (35.4%). At baseline, the mean systolic blood pressure was 133 mm Hg and mean diastolic blood pressure was 73 mm Hg, and 58.4% (n=98 869 with available blood pressure data) had a systolic blood pressure >130 mm Hg or diastolic blood pressure >80 mm Hg. The mean values of cholesterol, triglycerides, and hemoglobin A1c are also included in Table 1.

Table 2 shows baseline use of medications in our PAD cohort. Nearly two thirds (65.4%) of patients with PAD were on a statin at the time of PAD diagnosis, but only 31.2% were on a high-intensity statin. Among nonstatin lipid-lowering medications, use of ezetimibe (1.1%) and proprotein convertase subtilisin/kexin-9 inhibitors (<0.1%) at baseline were uncommon. Antiplatelet drugs were used in 35.0% (aspirin: 24.5%, P2Y12 inhibitors: 13.3%, and phosphodiesterase inhibitors: 3.0%) while anticoagulants were used in 12.9%

Table 2. Medications at Baseline in Study Cohort

	n=103 748
	n (%)
Lipid-lowering therapy	68 337 (65.9)
Statins	67 858 (65.4)
High-intensity statin	32 359 (31.2)
Ezetimibe	1141 (1.1)
PCSK-9	10 (0.0)
Antiplatelet agents*	36 312 (35.0)
Aspirin	25 449 (24.5)
P2Y12 Inhibitor	13 749 (13.3)
Phosphodiesterase inhibitor	3149 (3.0)
Anticoagulants	13 410 (12.9)
Warfarin	7116 (6.9)
NOAC	6501 (6.3)
Antihypertensive agents	84 226 (81.2)
ACE-I/ARB/ARNI	57 517 (55.4)
β-Blockers	49 484 (47.7)
Diuretics	42 963 (41.1)
Calcium channel blocker	31 708 (30.6)
Vasodilators	3758 (3.6)
α-Blocker	8728 (8.4)
Central acting	1887 (1.8)
Antidiabetic agents	42 826 (41.3)
Metformin	24 931 (24.0)
Insulin	22 952 (22.1)
DPP-4 inhibitors	3121 (3.0)
GLP-1 agonists	1441 (1.4)
SGLT-2 inhibitors	1430 (1.4)
Thiazolidinediones	1187 (1.1)
α-Glucosidase inhibitors	442 (0.4)
Meglitinides	97 (0.1)

Data in the table represents number (%). ACE-I indicates angiotensin-converting enzyme-inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin neprilysin inhibitor; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptides; NOAC, novel oral anticoagulant; PCSK-9, proprotein convertase subtilisin/kexin type 9; and SGLT-2, sodium glucose transporter-2.

*Aspirin may be underreported as it can be filled over the counter.

of patients (warfarin: 6.9%, novel oral anticoagulant: 6.3%). Only 25 patients (<0.1%) were taking low-dose rivaroxaban at baseline. Overall, 81.2% patients were receiving an antihypertensive with angiotensin converting enzyme-inhibitors, angiotensin receptor blockers, and angiotensin receptor neprilysin inhibitor being the most common medications. Among the 41.3% of patients receiving antidiabetic agents, metformin was the most common agent (24.0% patients) followed by sulfonylureas and insulin. Baseline use of glucagon-like peptide agonists and sodium glucose transporter-2 inhibitors was low.

The total number and the incidence (per 100 patient-years) of study end points are reported in Table 3 and Figure 2, respectively. Overall, 9723 participants (9.4%) died within 1 year of the index date. Among patient variables, older age, history of smoking, severity of PAD, and most comorbidities were strongly associated with higher risk of mortality, while female sex, Black race, and Hispanic ethnicity were associated with lower risk of 1-year mortality (Table 4). During 1-year follow-up, 2706 (2.6%) experienced an acute MI and 2881 (2.8%) experienced a stroke, 5249 (5.1%) experienced a CLI hospitalization, and 2616 (2.5%) underwent a major amputation. After accounting for the competing risk of mortality, the 1-year incidence rate of cardiovascular events was 5.6 per 100 patient-years (Figure 2A), which included acute MI (2.8 per 100 patient-years) and stroke (3.0 per 100 patient-years). The 1-year incidence of limb events was 7.0 per 100 patient-years (Figure 2B), which comprised hospitalization for CLI (5.5 per 100 patient-years) and major amputation (2.7 per 100 patient-years).

Table 3. Number of Patients Who Experienced a Study End Point at 1 Year

	1 year, n (%)
Mortality	9723 (9.4)
Cardiovascular events	5392 (5.2)
Acute myocardial infarction	2706 (2.6)
Stroke	2881 (2.8)
Limb events	6571 (6.3)
Critical limb ischemia	5249 (5.1)
Amputation	2616 (2.5)

Data in the table represent number (%).

Table S3 shows the proportion of nonfatal events identified using different data sources. Of the 5392 patients with a cardiovascular event (acute MI or stroke), 1721 (31.9%) were identified in the VHA, 2071 (38.4%) in Fee-basis (non-VA hospital claims paid by the VHA), 1177 (21.8%) and 423 (7.8%) in Medicare fee-for-service and Advantage, respectively. Among 6571 patients with a limb event (CLI or major amputation), 4791 (72.9%) were in the VHA, 925 (14.1%) in Fee-basis, 592 (9.0%) in Medicare fee-for-service, and 263 (4.0%) in Medicare Advantage claims.

DISCUSSION

Using a previously validated NLP system,[21] we have created a registry of >100 000 newly diagnosed patients with PAD in the VHA. In contrast to solely using administrative diagnosis and procedure codes that have modest accuracy,[17–20] identification of PAD in our cohort is based on abnormal ABI and TBI values, which are considered the criterion standard methods for clinical diagnosis of PAD.[28] Importantly, our cohort is racially and ethnically diverse with >19 000 (18.5%)

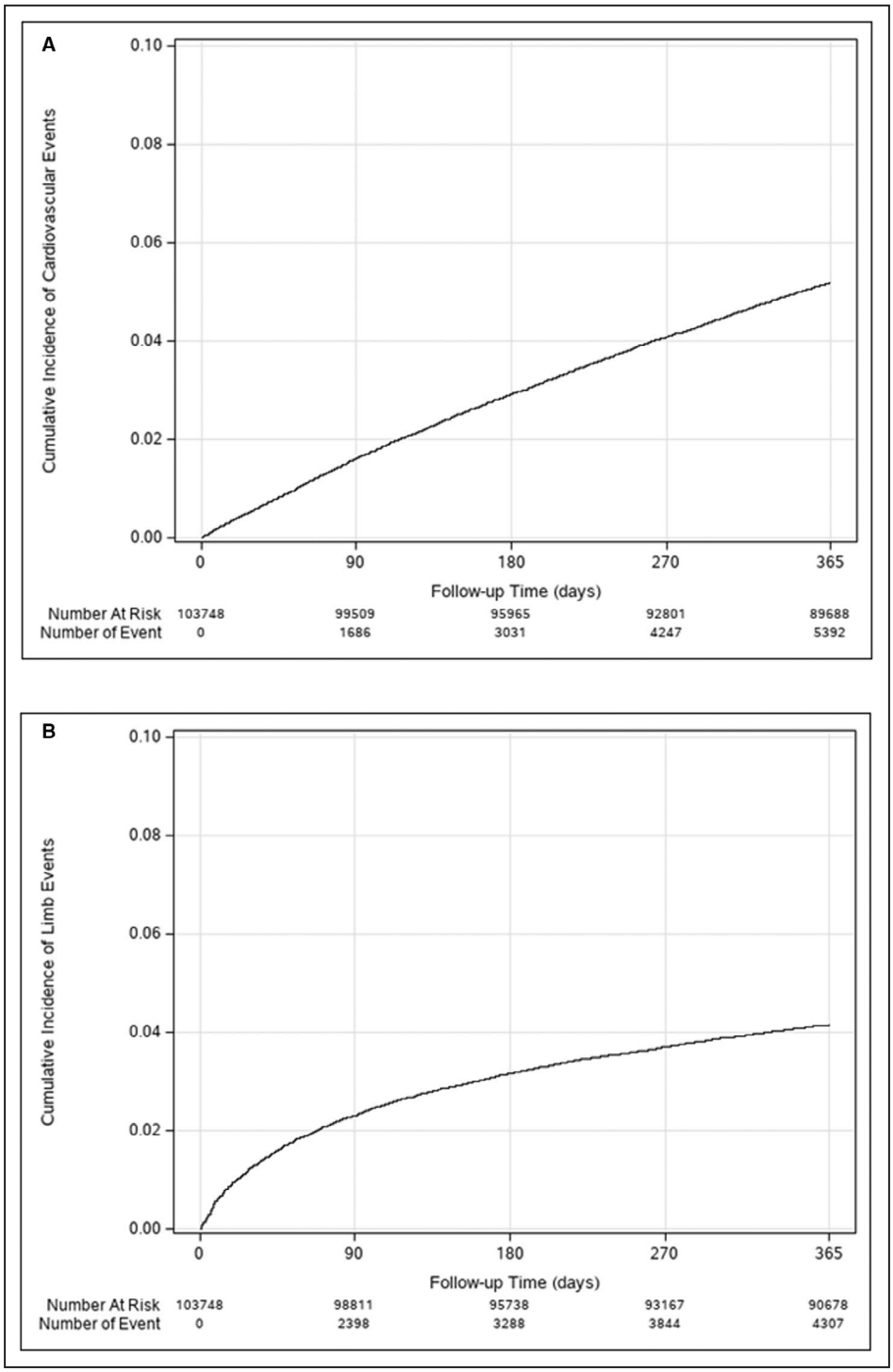

Figure 2. Cumulative incidence of cardiovascular events and limb events.
A, Shows the cumulative incidence of cardiovascular events (hospitalization for acute myocardial infarction or stroke) through 1 year. **B,** Shows the cumulative incidence of limb events (hospitalization for critical limb ischemia or amputation). The cumulative incidence function curves were estimated after accounting for competing risk of mortality.

individuals self-identified as Black, and >3000 (3.0%) self-identified as Hispanic. The prevalence of smoking and other comorbidities, including hypertension, coronary and cerebrovascular disease, diabetes, and chronic kidney disease was high. Rates of all-cause mortality approached 10% at 1 year, with high rates of cardiovascular and limb events, which underscore the enormous impact of PAD in real-world patients.

Table 4. Predictors of Mortality at 1 Year

Variable	Hazards ratio (95% CI)
Demographics	
Age groups, y (reference 40–49)	
50–59	1.69 (1.10–2.60)
60–69	2.07 (1.36–3.16)
70–79	2.54 (1.67–3.87)
≥80	5.04 (3.31–7.69)
Female sex	0.83 (0.70–0.97)
Black race	0.90 (0.85–0.95)
Hispanic or Latino	0.92 (0.82–1.04)
Smoking status (reference Non)	
Current	1.11 (1.03–1.19)
Former	1.04 (0.97–1.11)
Unknown	1.06 (1.00–1.14)
PAD severity (reference. Mild)	
Moderate	1.19 (1.13–1.26)
Severe	1.72 (1.63–1.82)
Comorbidities	
Hypertension	0.87 (0.81–0.93)
Diabetes	1.21 (1.16–1.27)
Chronic kidney disease	1.49 (1.43–1.56)
Chronic obstructive pulmonary disease	1.21 (1.16–1.26)
Arrhythmia	1.34 (1.28–1.40)
Heart failure	2.02 (1.93–2.13)
Coronary artery disease	0.95 (0.90–0.99)
Prior history of MI	1.19 (1.12–1.26)
Cerebrovascular disease	1.06 (1.01–1.11)
Cancer	1.32 (1.26–1.38)
Dementia	1.88 (1.77–1.99)
Depression	1.05 (1.00–1.09)
Chronic liver disease	1.34 (1.26–1.43)
Obesity	0.81 (0.77–0.86)
Anemia	1.29 (1.22–1.36)
Valvular heart disease	1.08 (1.03–1.14)
Weight loss	1.81 (1.71–1.91)

MI indicates myocardial infarction; and PAD, peripheral artery disease.

Prior studies of PAD in large health systems have been limited by the imprecision of ICD codes for identifying PAD. These studies have reported the sensitivity of *ICD* codes to range from 34.7% to 76.9% and the positive predictive value to range from 27.5% to 69.4%.[17–20] The low accuracy of *ICD* codes for PAD identification likely affects inferences drawn from such studies. To overcome this challenge, we developed an NLP system that can extract ABI and TBI values including laterality from ABI reports in the VHA.[21] An algorithm based on NLP-extracted ABI and TBI values had a higher sensitivity of 83.1% and positive predictive value of 92.3% as compared with *ICD* diagnosis and procedure codes for identifying PAD.[21] Building on this prior work, we now report the findings following the implementation of our NLP system in national VA data to develop an inception cohort of newly diagnosed PAD in the VHA during 2015–2020. The PEARLS cohort includes >100 000 Veterans with a new diagnosis of PAD, making it one of the largest contemporary cohorts of PAD to our knowledge. Importantly, linkage with an array of VA and non-VA data sources provides rich information on key variables (eg, smoking status, comorbidities, vital signs, laboratory values, and medications) as well as comprehensive follow-up. Thus, the PEARLS registry is well positioned to evaluate the long-term trajectory of health outcomes, examine the association of PAD treatments with long-term outcomes, and identify opportunities for improving care.

There are several advantages of studying PAD in the VHA. First, the VHA provides care to >9 million Veterans across 140 VA medical centers and 1138 outpatient sites that use a standardized EHR.[29] Risk factors for PAD, which include smoking, hypertension, and diabetes, are highly prevalent, leading to a high burden of PAD in Veterans. Second, although women are under-represented, our cohort still includes ≈3000 women, representing one of the largest contemporary cohorts of women with PAD. Importantly, racial and ethnic subgroups are well represented in our study with the inclusion of >19 000 Black individuals and ≈3000 Hispanic individuals, groups that have been under-represented in prior studies. Third, in addition to inpatient and outpatient claims, PEARLS also includes rich information on medications (VA Pharmacy and Part D claims), Vital Signs captured during clinical encounters, and Laboratory results that are generally unavailable in other cohorts. Most importantly, the availability of Fee-basis, Consolidated Dataset, and Medicare files ensures comprehensive follow-up data for defining clinical exposures (eg, medications) and clinical end points from VA and non-VA encounters (except the small minority of Veterans insured with commercial insurance plans).[30,31] This overcomes a key limitation of other EHR studies that are often limited in assessing events if they occurred in a different health system. Finally, VA data are updated nightly, providing real-time access avoiding delay inherent in studies that use other insurance claims data.

The high incidence of clinical events in our cohort underscores the substantial impact of PAD on patients. Nearly 10% of patients with PAD died within 1 year of diagnosis. Several patient variables including advanced age, male sex, severity of PAD, smoking, and comorbidities were associated with higher mortality, which is consistent with prior studies.[32] However, the negative association of Black race and Hispanic ethnicity with 1-year mortality in Veterans with PAD is in contrast to other studies that have shown worse outcomes in racial and ethnic minorities with PAD, which

may be due in part to access to health care, education, housing, and income in racial and ethnic minorities[33,34] The broad availability of comprehensive health coverage to all Veterans regardless of their income, education, or residence may be a potential explanation for these divergent findings, which needs further exploration.

The incidence of cardiovascular events was 5.6 per 100 patient-years at 1 year, accounting for competing risk of mortality, highlighting that PAD is a marker of malignant vascular phenotype with clinical event rates that far exceed those of patients with stable atherosclerotic cardiovascular disease.[35] For instance, among 32 961 patients with stable coronary artery disease, the prevalence of death or cardiovascular events was 7.6% at 5 years.[35] It was also striking that the incidence of limb events-hospitalization for CLI and major amputation was high as well (7.0 per 100 patient-years), approaching that of cardiovascular events. The downstream impact of a limb event (risk of infection, limited mobility, and disability) is enormous and contributes to high mortality and poor quality of life in patients with PAD. Thus, our findings support guideline recommendations, which consider abnormal ABI as a risk enhancer for primary prevention and the importance of developing strategies for not only evaluating therapies for reducing cardiovascular but also limb events.[36]

The use of an accurate method of identifying patients with PAD combined with rich and comprehensive data provides a unique opportunity to enhance contemporary PAD research in important ways. Ongoing studies from our cohort will yield important insights regarding patterns of care delivery for patients with PAD (eg, medications, risk factor control, and revascularization) and the extent to which these exposures are associated with long-term outcomes. Moreover, given the sizeable number of Black and Hispanic individuals in our cohort, we will also be able to evaluate whether disparities exist in care and outcomes of patients with PAD by race and ethnicity. Because health insurance is not a barrier in the VHA, we will also have a unique opportunity to isolate the contribution of access to health care from other social determinants of health in explaining disparities. These studies will be enabled with annual updates of clinical encounters from VA and non-VA (fee-basis, consolidated data set, and Medicare claims) as well as vital signs (mortality) that will be performed on an annual basis. Importantly, the large number of VA sites (≈140) also provides an opportunity to understand variation in care patterns across sites with the goal of identifying best practices.

Our study findings should be considered in the context of the following limitations. First, ABIs can be normal in patients with noncompressible vessels. If TBIs were measured in patients with noncompressible vessels, then such patients would be identified as PAD if the TBI value in any limb is ≤0.7. However, TBI measurements are not always performed. The NLP system would not be able to identify patients who did not have noncompressible vessels and who did not have TBI measured. Second, data on clinical symptoms and severity (eg, claudication and rest pain) are also not included. Because routine ABI screening of asymptomatic patients is not universally recommended, we expect that most patients in our cohort have symptomatic PAD. Third, we identified clinical end points using a combination of VA claims, non-VA claims paid by the VA, or Medicare claims to ensure near complete follow-up. However, it is possible that the incidence of clinical end points in younger Veterans not insured by Medicare or those with private insurance is underestimated. Fourth, medication data were based on prescriptions that were either filled at a VA pharmacy or using Medicare Part D insurance.[30,31] However, the VA provides generous pharmacy benefits for Veterans, which include (1) modest copayment not to exceed $11 per-month for all drugs including brand name medications, (2) no medication copayments for disabled Veterans with >50% service connection, medal-of-honor recipients or for treatment of conditions that are service connected even if they are covered <50%, (3) the convenience of mail-order and online pharmacy, and (4) annual out-of-pocket maximum copayment of $700. These incentives likely minimize the potential for missing information on medication exposures in our cohort.[37,38] Finally, due to its availability over the counter, use of aspirin may be underreported in our study.

CONCLUSIONS

We have successfully developed a registry of >100 000 patients with a new diagnosis of PAD in the VHA using a novel NLP algorithm. Ongoing studies from our cohort will yield important insights into the association between management of PAD and clinical outcomes, with the goal of identifying opportunities for improving care.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3
Figure S1

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