Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population

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Background: **Critical limb ischemia (CLI) represents the most severe clinical manifestation of peripheral arterial disease (PAD) and is the major cause of ischemic amputation in the United States. Risk factors and the associated incidence and prevalence of CLI have not been well described in the general population. This study describes the risk factors for PAD progression to CLI and estimates the annual incidence and prevalence of CLI in a representative United States patient cohort.**

Methods: **This was a retrospective cohort analysis of adults with commercial, Medicare supplemental, or Medicaid health insurance who had at least one PAD or CLI health care claim from January 1, 2003, through December 31, 2008, and 12 months of continuous coverage. Two subgroups of CLI presentation were identified: primary CLI (patients without any prior PAD or subsequent PAD diagnostic code >30 days after CLI diagnostic code) and secondary CLI (patients with prior PAD or subsequent PAD diagnostic codes ≤30 days of a CLI diagnostic code). Patterns of presentation, annual incidence, and prevalence of CLI were stratified by health care plan. Risk factors for progression to CLI were compared by presentation type.**

Results: **From 2003 to 2008, the mean annual incidence of PAD was 2.35% (95% confidence interval [CI], 2.34%-2.36%) and the incidence of CLI was 0.35% (95% CI, 0.34%-0.35%) of the eligible study population, with primary and secondary presentations occurring at similar rates. The mean annualized prevalence of PAD was 10.69% (95% CI, 10.67%10.70%) and the mean annualized prevalence of CLI was 1.33% (95% CI, 1.32%-1.34%) of the eligible study population, and two-thirds of the cases presented as secondary CLI. CLI developed in 11.08% (95% CI, 11.30%-11.13%) of patients with PAD. A multivariable model demonstrated that diabetes, heart failure, stroke, and renal failure were stronger predictors of primary rather than secondary CLI presentation.**

Conclusions: **These data establish new national estimates of the incidence and prevalence of CLI and define key risk factors that contribute to primary or secondary presentations of CLI within a very large contemporary insured population cohort in the United States. (J Vasc Surg 2014;60:686-95.)**

Although the prevalence of peripheral arterial disease (PAD) has been evaluated in several epidemiologic studies,[1-3] major knowledge gaps exist for critical limb ischemia (CLI). The population prevalence of PAD can be easily studied using standard epidemiologic approaches, with the ankle-brachial index serving as an objective measure of PAD.[4] A recent meta-analysis, in which pooled prevalence was calculated for men and women separately, estimated PAD prevalence in the United States ranged from 1.3% in men and 1.7% in women in from ages 40 to 49 years to as high as 29.5% in men and 24.7% in women aged >80 years.[5] Similar findings were observed in the National Health and Nutrition Examination Survey study cohort.[3]

In contrast, efforts to estimate the prevalence of CLI in population studies are challenging because the CLI

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diagnosis is clinically established by a constellation of lower extremity features, including ischemic rest pain and nonhealing ischemic wounds or gangrene, and requires the objective measurement of ankle or toe pressures. Few prior population-based studies have used such symptom and examination-based clinical criteria to define CLI incidence or prevalence.[6] Thus, in the absence of such data, establishing reliable estimates of the incidence and prevalence of CLI or demonstrating temporal incidence trends has been difficult.[7,8]

Current United States and international PAD practice guidelines have suggested that the annual incidence of CLI is 500 to 1000 cases/million people, but these estimates were largely based on older regional cohorts and limited survey studies of European populations.[9,10] In the absence of a common methodologic approach, a major CLI incidence and prevalence knowledge gap persists. There are no data to support the presumption that PAD follows a steady progression of severity and that few patients with claudication develop CLI.[11] Conversely, selected clinical cohort studies of patients with a history of ischemic amputation or revascularization for CLI have demonstrated a lack of any antecedent PAD symptoms or diagnosis in roughly half of these patients.[12-14] These observations have suggested that there may be different patterns of CLI presentation.

Large administrative claims databases have been used to examine a variety of trends in health care.[15-25] These databases have defined temporally increased rates of endovascular revascularization, stable to declining amputation rates, and racial and geographic vascular access health care disparities.[25,26] A recent study of the Medicare inpatient and outpatient database demonstrated an annual CLI incidence of 0.20% to 0.48% and an annual CLI prevalence of 0.23% to 0.54%, depending on a limited or expanded use of codes to define the same.[27] On the basis of this background, this study used national administrative claims database to examine estimates of PAD and CLI incidence, prevalence, patterns of presentation, and risk factors for progression to CLI.

METHODS

Study design and data source. A steering committee, including vascular specialty clinicians with CLI expertise, cardiovascular epidemiologists, and a biostatistician with expertise in large claims database analysis, was established to develop an independently managed protocol and statistical analysis plan, to review and select codes for PAD and CLI population identification, and to conduct the analysis. Authors A.H. and M.N., who were co-chairs for the steering committee, were selected to oversee the conduct of the study.

Data were obtained from the MarketScan database (Thomson Reuters [Healthcare] Inc, New York, NY) spanning the years 2003 to 2008 that included commercial, Medicare supplemental, and Medicaid populations. The MarketScan database contains detailed health services records derived from a set of large employers' health plans and from Medicare and Medicaid programs for millions of patients residing in many states across the country. MarketScan links billing and encounters data to detailed patient demographic and enrollment information across sites and types of providers and includes commercial health data from ~100 payers. The strengths of the database are that data are collected only when 100% of claims have been paid, improving the accuracy. Potential biases are inclusion of only Medicare beneficiaries who have supplemental insurance coverage (and may have access to better treatment), inclusion of employees only from large firms, and a geographic distribution that favors the central and southeastern United States.

In this retrospective cohort analysis, claims data for eligible patients (aged ≥40 years) were examined from 2003 to 2008. Each individual PAD or CLI case was identified on an "index diagnosis code date," defined as the first PAD or CLI diagnosis claim date identified in the period from January 1, 2004, through December 31, 2008. Further stratification was then applied to identify patients with a stable "prevalence period," defined as (1) a minimum 12-month period of continuous health insurance enrollment and (2) no PAD or CLI diagnosis code before the index date.

Examining a run-in prevalence period in claims research before the period during which the incidence is determined has been shown to improve the distinction between incident and prevalent cases.[28] Patients without an adequate 12-month prevalence run-in period before their PAD or CLI diagnosis code were excluded from further analysis. The observation period for each patient started on their "index diagnosis code date" and continued through December 31, 2008. Prevalent PAD and CLI cases were assessed beginning in 2003, with incident cases assessed beginning in 2004 to incorporate the prevalence period. Information was available on insurance enrollment, age, sex, and inpatient and outpatient diagnosis and procedure codes (Fig 1).

Code selection. Primary or secondary diagnosis International Classification of Diseases, Ninth Revision (ICD-9) codes and Current Procedural Terminology (CPT; American Medical Association, Chicago, Ill) codes were selected via a system designed to identify patients as having PAD with or without CLI within the following nonexclusive clinical categories: (1) PAD-specific codes or combination of codes, (2) CLI-specific codes or combination of codes, (3) PAD or CLI-specific lower extremity revascularization codes, and (4) major lower extremity amputation codes (Supplementary Table, online only). The following method was used to select the codes: First, ICD-9 and CPT coding manuals were used to identify all potentially relevant CPT and ICD-9 codes. Next, the steering committee reviewed the published PAD and CLI literature to determine the frequency of previous codes used to define claims-based PAD and CLI patients. From this review, relevant combination codes were selected to be more inclusive of probable PAD and CLI cases; for example, to include patients treated for an "ulcer" in combination with atherosclerosis, because this would not otherwise be captured as being related to CLI.

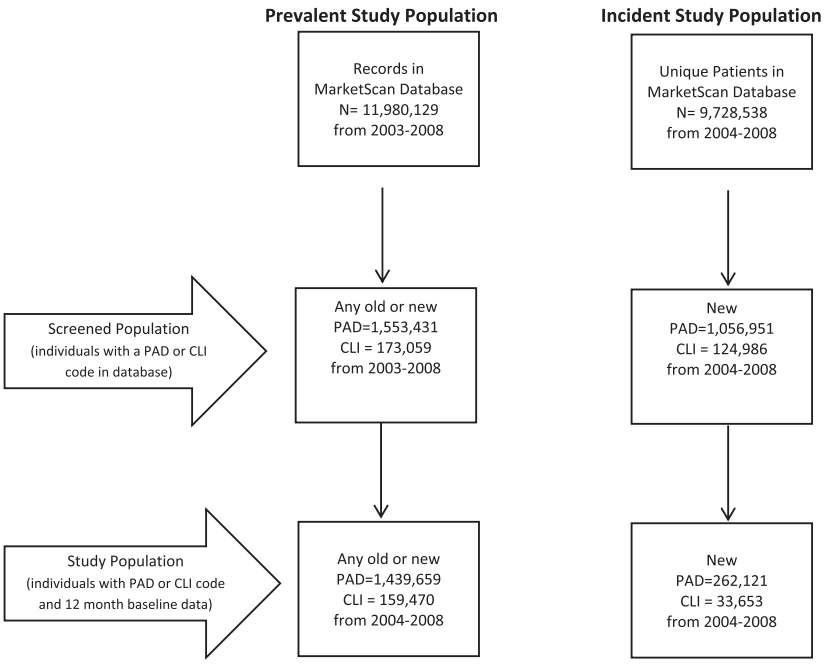

Fig 1. Cohort assembly to define prevalent and incident study populations. *CLI,* Critical limb ischemia; *PAD,* peripheral arterial disease.

Codes selected to be inclusive were reviewed to define their overall contribution to the final identified population. A similar strategy to increase CLI coding yields has been demonstrated previously.[27] Final selection of codes by steering committee members was designed to be maximally inclusive of codes for atherosclerotic lower extremity PAD and exclusive of codes that defined acute thrombosis or embolism, and arterial disease of the upper extremity, carotid, and mesenteric arteries. These code categories are presented in the Supplementary Table, online only.

Index cases of PAD or CLI were defined according to the following clinical categories of codes: PAD, CLI, lower extremity revascularization, and lower extremity major amputation. Specific code linkage criteria were further applied to define cases as PAD or CLI. Ischemic rest pain was defined exclusively using the specific code for same (440.22) to exclude other causes of extremity pain. Combination codes were used for CLI, as an example, so that lower extremity wound codes were included within the CLI clinical category only if present in combination with subsequent ICD-9 codes that were specific to lower extremity PAD (440.20, 440.21, 440.22, 440.23, and 440.24). Similarly, codes specific to lower extremity revascularization were included within the CLI clinical category only if present in combination with more specific subsequent codes, such as atherosclerosis with gangrene, ulceration, or rest pain (ICD-9 codes 440.24, 440.23, 440.22). All other revascularization codes were included in the PAD (non-CLI) category. Codes specific to major lower extremity amputation were considered stand-alone codes for CLI and did not require linkage with an ICD-9 code specific to atherosclerosis to be included in the CLI category. In addition, cancer and trauma-related ICD-9 or CPT codes were used to exclude non-CLI causes of leg amputation.

Once the codes were identified, patients were assigned into three mutually exclusive groups: PAD without having an associated CLI code, PAD progressing to CLI (secondary CLI) where the CLI code occurred >30 days after the PAD code, and primary CLI where the CLI code occurred without a concomitant PAD code or the PAD code was noted ≤30 days after the CLI code. Table I reports these three patient study groupings for the described prevalent and incident examples.

Patient characteristics and comorbidities. Study population comorbidities, based on predefined ICD-9 codes, were selected in a manner similar to the code selection for PAD and CLI described above. Most comorbid conditions were included if present before the index date of PAD or CLI. However, diabetes was defined as a baseline comorbidity if present before the index date of PAD or CLI or at any time during the observation period because of the inherent discrepancy between the "onset" of diabetes and the imprecise timing of related ICD-9 codes in a claims database.

Incidence and prevalence calculations. The annual prevalence of PAD and CLI from 2003 to 2008 was calculated as the number of patients with PAD or CLI at a specific year, divided by the total eligible population during that same year. The eligible population varied annually

Table I. Categorization of peripheral arterial disease (*PAD*) and critical limb ischemia (*CLI*) patients[a]

Variable	*PAD+/CLI− (PAD)*[b]	*PAD+/CLI+ (secondary CLI)*[c]	*PAD−/CLI+ (primary CLI)*[d]	*Total*[e]
Prevalent cases with any code in 2004	PAD without CLI (n = 141,094) or RV code without amputation or wound (n = 8160)	PAD code and: CLI code or Amputation code or RV and CLI code	CLI code or Amputation code or RV and CLI code	
No.	149,254	11,563	7,732	168,549
	PAD+/CLI− (PAD)	*PAD+/CLI+ (secondary CLI) PAD precedes CLI*	*PAD−/CLI+ (primary CLI) CLI precedes PAD*	
Incident cases with new codes from 2004-2008	Index event first time new PAD with no CLI code (n = 183,110) First time new RV with no CLI code (n = 45,358)	Index event first time PAD code with new CLI code occurring >30 days after PAD code (n = 18,081)	Index event first time CLI (n = 15,572) without concurrent PAD code Index event first time amputation (n = 2679) without concurrent PAD code	
No.	228,468	15,402	18,251	262,121

RV, Revascularization.
[a]Baseline prevalence was described in 2004, the first year of the study.
[b]PAD+/CLI− is a PAD code without a CLI code (PAD).
[c]PAD+/CLI+ is a PAD code predating or ≤30 days after a CLI code (secondary CLI).
[d]PAD−/CLI+ is a CLI code without a predating PAD code or subsequent PAD code ≤30 days subsequent to the CLI code (primary CLI).
[e]Total is the sum of the three mutually exclusive vascular disease groups.

due to inclusion of new enrollees and loss of individuals who did not continue within their health insurance coverage plan. The annual incidence was calculated as the number of individuals with a new PAD or new CLI ICD-9 or CPT code within the eligible population at risk during a specific year, divided by the total eligible population at risk at the beginning of the same year.

Statistical analysis. For all analyses, longitudinal data sets with one record per individual from 2003 to 2008 were created. Descriptive statistics are presented with continuous variables reported as mean values (standard deviation) and categoric variables reported as proportions. Estimates of PAD and CLI prevalence and incidence are presented as percentages. Average prevalence and incidence values were determined across the 6 years of observation (with a 1-year baseline of continuous coverage that was free of vascular disease) by using a weighted averaging technique and are presented with 95% confidence intervals (CIs).

Risk factors for primary and secondary CLI were first considered as univariate factors that included age, sex, diabetes, hypertension, obesity, myocardial infarction, stroke, heart failure, and renal failure. Univariate associations with a P value of $<.10$ were included in a multivariable model adjusted for age and sex to predict which factors were independently associated with developing CLI. Data extraction and analysis was conducted using SAS 9.2 software (SAS Institute Inc, Cary, NC).

RESULTS

Cohort assembly. Fig 2 shows the relative proportion of major codes that served as contributors to the incident PAD index case ascertainment: Almost three-quarters were due to codes specific to "atherosclerosis" and "other peripheral vascular disease," and 13% had a CLI code for primary or secondary presentation. A breakdown of the contribution to the two CLI presentation subgroups showed most of the index cases for both were due to atherosclerosis with ulceration, followed by atherosclerosis and rest pain, and the remainder were due to atherosclerosis and gangrene or atherosclerosis and amputation. Amputation codes were more prominent in primary CLI than in secondary CLI.

Baseline demographics and comorbidities in prevalent and incident populations. Baseline demographics and comorbidities were derived from 2004, which was the first full year of patient identification and follow-up. Table II, *A* describes the incident population and Table II, *B* the prevalent population. In the 2004 incident population, age was similar across the three groups (Table II, *A*). Incident secondary CLI patients were more likely receiving Medicaid than the PAD patients for the PAD and primary

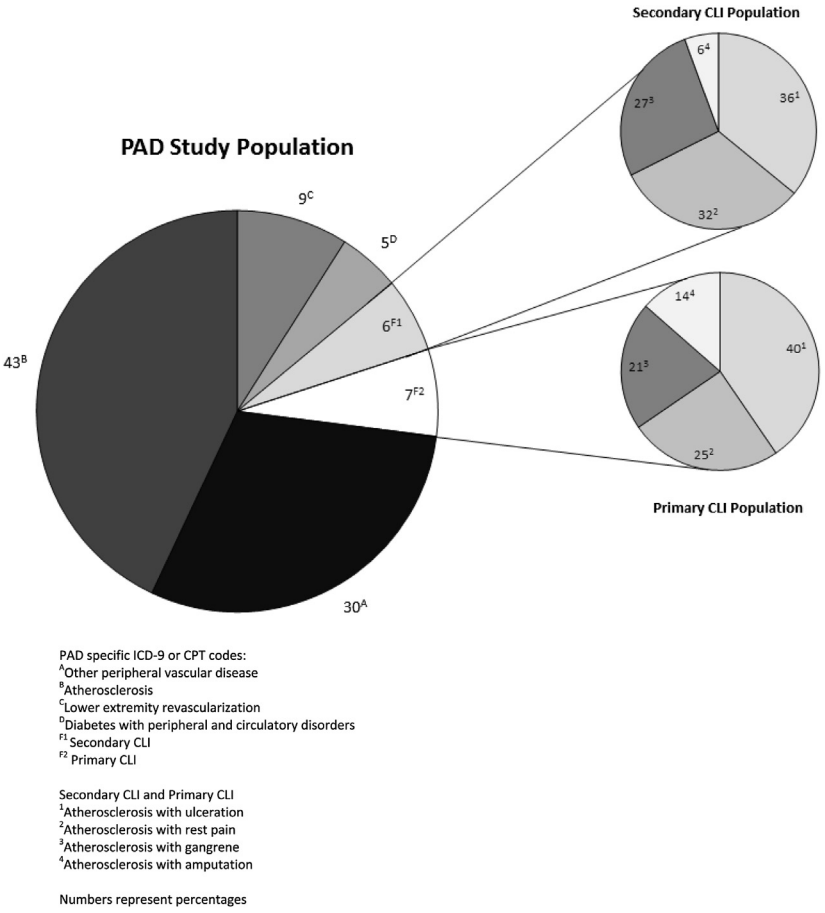

Fig 2. Code distribution for peripheral arterial disease (*PAD*) and critical limb ischemia (*CLI*) subgroups. *CPT,* Current Procedural Terminology (American Medical Association, Chicago, Ill); *ICD-9,* International Classification of Diseases, Ninth Revision.

CLI groups. Primary CLI patients were more likely receiving commercial insurance than secondary CLI patients. There were no age differences among the three groups.

In 2004, the prevalent secondary CLI patients were slightly older and more likely to be insured by Medicaid than the PAD patients (Table II, *B*). In contrast, prevalent primary CLI patients were younger and more likely to be covered by commercial insurance than PAD patients. Prevalent patients who had secondary CLI had the highest prevalence of cardiovascular risk factors, PAD was intermediate, and primary CLI had the lowest density of risk factors.

Annual incidence of PAD and CLI in the study population. Table III provides disease incidence by year and type of coverage. The respective mean annual incidence of PAD was 2.35% (95% CI, 2.34%-2.36%), secondary CLI was 0.16% (95% CI, 0.16%-0.16%), primary CLI was 0.19% (95% CI, 0.18%-0.19%), and all CLI was 0.35% (95% CI, 0.34%-0.35%). The commercial insurance population had a lower incidence of PAD and CLI than individuals covered by Medicaid and Medicare.

Annual prevalence of PAD and CLI in the study population. Table IV provides disease prevalence by year and type of coverage. The respective overall mean annual prevalence of PAD was 10.69% (95% CI, 10.67%-10.7%), secondary CLI was 0.86% (95%, CI 0.86%-0.87%), primary CLI was 0.47% (95% CI, 0.46%-0.47%), and all CLI was 1.33% (95% CI, 1.32%-1.34%). All CLI represented 11.08% (95% CI, 11.03%-11.13%) of total PAD annually. PAD and CLI prevalence was generally lower in patients with commercial insurance than in those covered by Medicaid and Medicare.

Risk factors for secondary CLI. Univariate predictors for secondary CLI in patients with PAD included age at time of PAD diagnosis, male gender, diabetes, and a history of myocardial infarction, stroke, heart failure, or renal failure (Table V). Hypertension was associated with a decreased risk of developing secondary CLI. A multivariable model demonstrated an increased risk for secondary CLI was associated with diabetes (odds ratio [OR], 2.33), stroke (OR, 1.22), and heart failure (OR, 1.36), with hypertension minimally lowering this risk (OR, 0.93).

Table II. A, Incidence population for peripheral arterial disease (*PAD*) and critical limb ischemia (*CLI*) subgroups: baseline demographic characteristics and comorbidities of the study population in 2004 to 2008

	Incidence population[a]			
Demographic characteristics	*PAD*[b] *(n = 228,468)*	*Secondary CLI*[c] *(n = 15,402)*	*Primary CLI*[d] *(n = 18,251)*	*Total*[e] *(N = 262,121)*
Age, mean ± SD years	68.9 ± 12.5	69.3 ± 12.6	69.0 ± 13.4	68.9 ± 12.6
Age group, years, %				
40-49	6.4	6.4	7.9	6.5
50-59	19.3	19.2	20.4	19.4
60-69	25.3	23.8	22.7	25.0
70-79	12.1	12.2	10.6	12.0
80-84	24.8	25.7	23.4	24.8
≥85	12.0	12.7	15.1	12.2
Gender, %				
Male	43.7	47.8	46.1	44.1
Female	56.3	52.2	53.9	55.9
Type of health plan, %				
Commercial	28.3	20.1	28.5	27.8
Medicaid	30.5	40.6	29.5	31.0
Medicare supplemental	41.2	39.3	42.0	41.2
Patients with ≥1 comorbidity, %	94.9	95.7	91.8	94.7
Diabetes	14.7	31.6	28.5	16.7
Hypertension	72.2	70.9	66.5	71.7
Myocardial infarction	43.3	41.8	34.5	42.6
Stroke	19.7	22.0	19.0	19.8
Heart failure	21.6	30.0	25.6	22.4
Renal failure	8.9	13.3	11.0	9.3
Cancer	14.5	9.6	11.3	14.0

SD, standard deviation.
[a]Incidence population: Adults ≥40 years with a PAD or CLI International Classification of Diseases, 9th Revision (ICD-9) or Current Medical Terminology (CPT; American Medical Association, Chicago, Ill) code in the MarketScan database (Thomson Reuters [Healthcare] Inc, New York, NY) between 2004 and 2008, and with continuous 12-month baseline coverage.
[b]Incident PAD defined codes without CLI codes.
[c]Incident CLI defined codes with a prior PAD diagnostic code and/or subsequent PAD code ≤30 days of CLI code.
[d]Incident CLI defined codes without a prior PAD diagnostic code or subsequent PAD code ≤30 days of CLI code.
[e]Total (PAD and CLI codes combined).

Risk factors for primary CLI. Univariate predictors for primary CLI in patients without PAD included age at initial assessment, male gender, diabetes, hypertension, and a history of myocardial infarction, stroke, heart failure, or renal failure (Table VI). A multivariable model demonstrated all of the univariate positive risk associations remained statistically significant, with diabetes being markedly predictive (OR, 7.45).

DISCUSSION

These data establish new estimates of the annual incidence and prevalence for PAD and CLI within the MarketScan database, a very large insured national population surrogate. In the eligible population, PAD had an annual incidence of 2.35% and an average annual prevalence of 10.69%, and CLI had an annual incidence of 0.35% and an average prevalence of 1.33%. Annually, 11.08% of patients with PAD had CLI.

The PAD estimates from this insured population are concordant with established population-derived data. The incidence of CLI in this study is consistent with a recent Medicare database report citing 0.2% to 0.4%, depending on a narrow or broad range of code inclusion.[27] Conversely, it is significantly higher than the incidence rate reported as 220 cases/1 million people (0.022%) in a large prospective population study[29] and is also higher than incidence rates cited in the TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) guidelines of 500 to 1000/1 million people (0.05%-0.1%).[30] The prevalence of CLI in patients with PAD in this study is also slightly higher than described in the TASC II guidelines (3%-10% overall).[20] The TASC II guidelines data are derived from data nearly 2 decades old and rely on surveys or longitudinal data with small sample sizes for short periods of time within defined regional areas.[6,10] In contrast, the current analysis is based on a very large, geographically diverse national population and includes markedly greater numbers of PAD and CLI individuals examined over a long duration.

Finally, the prevalence of CLI in the current trial is roughly three times greater than the 0.23% to 0.54% cited in a recent Medicare database review.[27] However, some of this discrepancy could be explained by the exclusion of all patients in the Medicare study without 12 months of continuous follow-up data, which, given the annual

Table II. B, Prevalence population for peripheral arterial disease (*PAD*) and critical limb ischemia (*CLI*) subgroups: baseline demographic characteristics and comorbidities of the study population in 2004

	Prevalent population[a]			
Demographic characteristics	*PAD*[b] *(n = 149,254)*	*Secondary CLI*[c] *(n = 11,563)*	*Primary CLI*[d] *(n = 7732)*	*Total PAD*[e] *(N = 168,549)*
Age, mean ± SD, years	68.9 ± 12.5	69.7 ± 12.6	66.3 ± 13.9	68.9 ± 12.6
Age group, years, %				
40-49	7.2	6.4	12.6	7.4
50-59	17.7	17.1	23.3	17.9
60-69	24.3	24.0	21.9	24.2
70-79	13.4	12.9	10.2	13.2
80-84	26.5	26.5	20.1	26.2
≥85	11.0	13.2	11.7	11.1
Sex, %				
Male	46.4	52.6	48.7	46.9
Female	53.6	47.4	51.3	53.1
Type of health plan, %				
Commercial	30.4	24.7	39.5	30.4
Medicaid	20.4	27.0	19.5	20.8
Medicare supplemental	49.2	48.3	41.0	48.8
Patients with ≥1 comorbidity, %	77.9	89.9	72.1	78.5
Diabetes	13.2	42.6	20.5	15.6
Hypertension	53.7	61.5	47.1	53.9
Myocardial infarction	33.6	42.3	23.4	33.8
Stroke	14.3	20.2	11.6	14.6
Heart failure	15.0	29.6	17.2	16.1
Renal failure	2.8	8.1	3.7	3.2
Cancer	8.6	7.3	7.8	8.5

SD, Standard deviation.

[a]Prevalent population: Adults ≥40 years with a PAD or CLI International Classification of Diseases, 9th Revision (ICD-9) or Current Medical Terminology (CPT; American Medical Association, Chicago, Ill) code in the MarketScan database (Thomson Reuters [Healthcare] Inc, New York, NY) in 2004 with 12 months of continuous eligible insurance coverage during the 2003 baseline period.

[b]PAD defined codes without CLI codes.

[c]CLI defined codes with a prior PAD diagnostic code or subsequent PAD code ≤30 days of CLI code, or both.

[d]CLI defined codes without a prior PAD diagnostic code or subsequent PAD code ≤30 days of CLI code.

[e]Total (PAD and CLI combined).

mortality in CLI, likely excluded patients captured in the current study. The current CLI prevalence is, however, not markedly different than the pooled CLI prevalence of 0.8% in a recent meta-analysis.[31] A study examining the geographic breakdown of CLI prevalence did favor the southeastern United States, which has biased representation in the MarketScan database.[32]

This study demonstrates that CLI prevalence was higher in the Medicare and Medicaid cohorts compared with the commercial payer population, consistent with the increased age and comorbid diseases (eg, diabetes, chronic kidney disease) that are present in these particular insured populations. The patterns of CLI coding presentations were distinguished in the current study as primary or secondary cases. That patients with claudication infrequently progress to CLI when followed up longitudinally is well known.[33] Prior small series of CLI patients who undergo a revascularization procedure or amputation have demonstrated that at least half of these patients had no recognized PAD symptoms or diagnosis in the 6 months before CLI presentation.[28,29] These reports suggest that the presentation patterns of CLI are not uniform. This study supports this concept, because risk factors, presentation, and outcomes of individuals with the primary vs secondary presentations are not identical.

Risk factors for secondary CLI were consistent with previous CLI reports and support the critical role of age, male gender, and pre-existing cardiovascular disease as key predictors of a poor outcome of PAD. Risk factors for primary CLI demonstrated stronger associations for all risk factors, especially diabetes. This analysis could imply a potential etiologic difference between individuals who present with primary vs secondary CLI syndromes. Hypertension, for example, was associated with a reduced risk of developing secondary CLI, which is consistent with prior data demonstrating that hypertension is sometimes associated with improved foot perfusion and partially ameliorating CLI symptoms. In contrast, hypertension, as coded in our study, was associated with an increased risk of developing primary CLI, and it is possible that when hypertension is clinically recognized, treated pharmacologically, and coded, this diagnosis may be associated with a lower risk of developing secondary CLI

Table III. Incidence of peripheral arterial disease (*PAD*) and critical limb ischemia (*CLI*) subgroups, overall and by health insurance plan at each year (2004 to 2008)

			Incidence			
Group	*Year*	*Eligible risk population,*[a] *No.*	*PAD,*[b] *%*	*Secondary CLI,*[c] *%*	*Primary CLI,*[d] *%*	*Total,*[e] *%*
Overall	2004	1,638,930	2.19	0.24	0.18	2.61
	2005	1,744,766	2.83	0.23	0.23	3.29
	2006	1,366,794	3.05	0.21	0.23	3.48
	2007	2,275,054	1.83	0.10	0.14	2.07
	2008	2,702,994	2.22	0.09	0.18	2.49
Mean (95% CI)			2.35 (2.34-2.36)	0.16 (0.16-0.16)	0.19 (0.18-0.19)	2.69 (2.68-2.70)
Commercial	2004	837,108	0.88	0.06	0.08	1.02
	2005	848,702	1.50	0.09	0.13	1.72
	2006	672,715	1.31	0.07	0.10	1.48
	2007	1,472,776	0.81	0.03	0.06	0.91
	2008	1,829,209	1.29	0.05	0.10	1.45
Medicaid	2004	278,509	4.99	0.71	0.40	6.10
	2005	364,475	3.78	0.39	0.28	4.45
	2006	318,395	5.66	0.43	0.43	6.52
	2007	247,785	4.95	0.33	0.33	5.62
	2008	251,551	4.65	0.26	0.42	5.34
Medicare supplemental	2004	523,313	2.78	0.27	0.24	3.30
	2005	531,589	4.30	0.33	0.35	4.98
	2006	375,684	3.93	0.26	0.30	4.50
	2007	554,493	3.13	0.17	0.26	3.56
	2008	622,234	3.95	0.15	0.32	4.42

CI, Confidence interval.
[a]Adults aged >40 years with commercial, Medicare supplemental, or Medicaid health insurance, without evidence of symptomatic PAD or CLI at any given year between 2004 and 2008.
[b]Total number of new PAD without CLI at a given year, divided by the eligible population at risk during the same year.
[c]Total number of individuals with first occurrence of an International Classification of Diseases, 9th Revision (ICD-9) or Current Medical Terminology (CPT; American Medical Association, Chicago, Ill) CLI code who also had a pre-existing PAD code or a subsequent PAD code ≤30 days in a given year, divided by the eligible population at risk during the same year.
[d]Total number of individuals with first occurrence of an ICD-9 or CPT CLI code without a pre-existing PAD code or a subsequent PAD code ≤30 days.
[e]Total number in all three groups (PAD, primary CLI, secondary CLI) in a given year, divided by the total number of individuals without evidence of symptomatic PAD or CLI during the same year.

(ie, the diagnosis is linked to better blood pressure control and less PAD progression).

Limitations. This study has several limitations, including the lack of independent validation of the codes via medical record review. The analysis excluded large numbers of patients due to lack of 12-month baseline data, with possible bias due to mechanisms that cause coverage change. However, these design features would all result in an underestimation of CLI incidence and prevalence rates. Future analyses would also benefit from including an uninsured patient population.

The methodology used in this study may also overestimate CLI rates because of the effort to use an inclusive list of billing codes. This is unique compared with most of the coding literature on this subject that limits CLI to the three codes linking atherosclerosis to rest pain, ulceration, or gangrene. The use of all major amputations as a surrogate for CLI includes the minority of amputations performed for diabetic neuropathy and major foot infections with normal arterial circulation, which may represent ~10% of all major amputations according to prior reviews.[12,34] These assumptions were used for the study to be maximally inclusive given the relatively nonspecific nature of CLI administrative coding.

The 30-day cutpoint to distinguish primary vs secondary CLI was arbitrary, and alternate cutpoints would shift the fraction of individuals in each post hoc assigned CLI category.

Major strengths of our study include the very large sample, the rigorous review, and the selection of diagnosis codes. Although no prior study has performed a clinical validation of the use of ICD-9 and CPT codes to accurately define PAD and CLI case rates, the code selection method described herein could be considered as a common approach for future analyses.

Finally, the use of the MarketScan database introduces some bias. The geographic distribution favors the central and southeastern United States, where CLI risk factors may be greater. The data for Medicare patients represent only those patients with supplemental coverage. The data from commercial insurance only represent employees from large firms. The database does not include uninsured patients.

Table IV. Prevalence of peripheral arterial disease (*PAD*) and critical limb ischemia (*CLI*) subgroups overall and by health insurance plan by year

			Prevalent PAD or CLI, or both, in total population				
Group	*Year*	*Eligible population,[a] No.*	*PAD,[b] %*	*Secondary CLI,[c] %*	*Primary CLI,[d] %*	*Total PAD,[e] %*	*Total CLI in PAD,[f] %*
Overall	2003	1,106,701	11.13	1.20	0.59	12.92	13.84
	2004	1,791,587	8.33	0.65	0.43	9.41	11.45
	2005	1,952,043	10.39	0.88	0.46	11.73	11.38
	2006	1,551,643	12.17	1.01	0.50	13.67	11.02
	2007	2,547,638	11.09	0.80	0.45	12.34	10.17
	2008	3,030,517	11.01	0.83	0.45	12.29	10.46
Mean (95% CI)			10.69 (10.67-10.70)	0.86 (0.86-0.87)	0.47 (0.46-0.47)	12.02 (12.00-12.04)	11.08 (11.03-11.13)
Commercial	2003	465,613	6.34	0.52	0.40	7.27	12.70
	2004	881,759	5.14	0.32	0.35	5.81	11.53
	2005	900,071	5.90	0.39	0.33	6.62	10.87
	2006	707,813	5.93	0.37	0.29	6.58	10.01
	2007	1,575,641	7.35	0.41	0.35	8.11	9.34
	2008	1,961,237	7.28	0.45	0.35	8.09	9.94
Medicaid	2003	287,429	14.54	1.89	0.73	17.16	15.24
	2004	310,506	9.81	1.01	0.49	11.30	13.20
	2005	426,573	13.76	1.52	0.59	15.87	13.30
	2006	382,087	16.27	1.66	0.62	18.55	12.32
	2007	300,951	17.50	1.77	0.69	19.97	12.33
	2008	306,389	17.66	1.89	0.68	20.23	12.72
Medicare	2003	353,659	14.66	1.52	0.73	16.91	13.33
	2004	599,322	12.26	0.93	0.53	13.72	10.65
	2005	625,399	14.56	1.13	0.56	16.25	10.40
	2006	461,743	18.34	1.45	0.71	20.50	10.54
	2007	671,046	16.98	1.29	0.59	18.86	9.98
	2008	762,891	17.91	1.40	0.61	19.92	10.08

CI, Confidence interval.
[a]Adults aged ≥40 years with commercial, Medicare supplemental, or Medicaid health insurance, from January 1, 2003, through December 31, 2008.
[b]PAD patients without CLI in a given year, divided by the eligible population in that year.
[c]PAD patients with a prior PAD diagnostic code or subsequent PAD code ≤30 days of CLI code in a given year, or both, divided by the eligible population in that year.
[d]CLI patients without a prior PAD diagnostic code or subsequent PAD code ≤30 days of CLI code in a given year, divided by the eligible population in that year.
[e]Sum of PAD, primary CLI and secondary CLI patients, divided by the eligible population in that year.
[f]Total number of primary and secondary CLI patients, divided by the total number of PAD patients in that year.

Table V. Risk factors for progression from peripheral arterial disease (PAD) to critical limb ischemia (CLI), indicated as secondary CLI[a]

	OR (95% CI)	
Risk factor	*Univariate*	*Multivariable[b]*
Age at time of diagnosis	1.007 (1.005-1.009)	1.008 (1.006-1.010)
Male gender	1.153 (1.102-1.208)	1.185 (1.131-1.241)
Diabetes	2.353 (2.237-2.475)	2.331 (2.211-2.458)
Hypertension	0.986 (0.937-1.038)	0.927 (0.880-0.976)
Myocardial infarction	1.068 (1.020-1.119)	0.942 (0.898-0.989)
Stroke	1.296 (1.228-1.368)	1.217 (1.152-1.285)
Heart failure	1.576 (1.499-1.657)	1.362 (1.292-1.435)
Renal failure	1.336 (1.244-1.435)	0.969 (0.899-1.045)

CI, Confidence interval; *OR,* odds ratio.
[a]Secondary CLI defined as a new CLI diagnostic code occurring in a patient with a pre-existing PAD code or a PAD code occurring ≤30 days after the CLI code (n = 15,572).
[b]The multivariate model included age and gender as adjustment variables.

Table VI. Risk factors for progression to new critical limb ischemia (CLI) without peripheral arterial disease (PAD; primary CLI)[a]

	OR (95% CI)	
Risk factor	*Univariate*	*Multivariable[b]*
Age at time of assessment	1.075 (1.074-1.076)	1.051 (1.050-1.052)
Male gender	1.079 (1.048-1.110)	1.075 (1.043-1.107)
Diabetes	19.682 (19.058-20.328)	7.452 (7.191-7.723)
Hypertension	5.081 (4.927-5.240)	2.430 (2.353-2.510)
Myocardial infarction	6.891 (6.684-7.105)	1.855 (1.792-1.921)
Stroke	8.974 (8.647-9.313)	2.168 (2.083-2.256)
Heart failure	13.929 (13.472-14.402)	2.273 (2.185-2.365)
Renal failure	14.122 (13.479-14.795)	1.866 (1.772-1.965)

CI, Confidence interval; *OR,* odds ratio.
[a]Primary CLI defined as a new CLI diagnostic code occurring in a patient without a pre-existing PAD code or a PAD code occurring ≤30 days after the CLI code (n = 18,251).
[b]The multivariate model included age and gender as adjustment variables.

CONCLUSIONS

As the population continues to age, the methods used in this study could be used to provide population-based surveillance of PAD and CLI and to project health resource utilization. Finally, these data could be useful for the planning and execution of future PAD and CLI clinical trials and registries.

AUTHOR CONTRIBUTIONS

Conception and design: MN, SD, AH, WH, AZ, BA
Analysis and interpretation: MN, SD, LD, KR, AZ, BA, WH
Data collection: LD, AZ
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Critical revision of the article: MN, SD, AH, KR, WH, LD
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Obtained funding: WH
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Additional material for this article may be found online at www.jvascsurg.org.

Supplementary Table (online only). International Classification of Diseases-9th Revision (*ICD-9*) and Current Procedural Terminology (*CPT*) codes[a] used to identify peripheral arterial disease (*PAD*) and critical limb ischemia (*CLI*) patients

Category	*Diagnosis/procedure*	*Associated ICD-9 or CPT codes*	*Frequency of occurrence (%)*
PAD diagnosis	Other peripheral vascular disease	ICD-9: 443.1, 443.22, 443.81, 443.89, 443.9	38.29
	Atherosclerosis	ICD-9: 440.0, 440.20, 440.21, 440.29, 440.30, 440.31, 440.32, 440.4, 440.8, 440.9	18.02
	Diabetes with peripheral circulatory disorders	ICD-9: 249.70, 249.71, 250.70, 250.71, 250.72, 250.73	8.40
	Chronic ulcer of skin	ICD-9: 707.06, 707.07	3.18
	Other disorders of arteries	ICD-9: 447.1	2.99
	Atheroembolism	ICD-9: 445.02	0.08
CLI diagnosis	Pain in limb	ICD-9: (729.5)[b]	4.29
	Gangrene	ICD-9: 785.4	3.29
	Ulcer of lower limb	ICD-9: (707.1, 707.10, 707.13, 707.14, 707.15, 707.19, 707.9)[b]	3.05
	Atherosclerosis (with rest pain, gangrene, or ulceration)	ICD-9: 440.22,440.23,440.24	1.46
	Excision/debridement	ICD-9: (77.65, 77.66, 77.67, 77.68, 86.22, 99.10)[b]	0.30
	Postoperative wound infection	ICD-9: (998.59)[b]	0.25
	Acute osteomyelitis of lower limb	ICD-9: (730.06, 730.07)[b]	0.21
	Chronic osteomyelitis of lower Limb	ICD-9: (730.16, 730.17)[b]	0.14
Lower extremity revascularization	Percutaneous transluminal angioplasty	ICD-9: 00.40, 00.41, 00.42, 00.43, 00.44, 39.50; CPT: 354542, 35454, 35456, 35459, 35470, 35472, 35473, 35474	4.47
	Peripheral Bypass	ICD-9: 39.25, 39.29; CPT: 35500, 35521, 35533, 35537, 35538, 35539, 35540, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35583, 35585, 35587, 35621, 35623, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 35681, 35682, 35700, (35683, 35686, 35571)[c]	1.60
	Stents	ICD-9: 39.90, 00.45, 00.46, 00.47, 00.48, 00.55	0.85
	Other lower extremity revascularization	ICD-9: 38.08, 39.49; CPT: 35221, 35226, 35256, 35286	0.56
	Endarterectomy	ICD-9: 38.16, 38.18, 38.38, 38.48, 38.68; CPT: 35302, 35303, 35304, 35305, 35306, 35331, 35351, 35355, 35361, 35363, 35371, 35372, 35381	0.54
	Atherectomy	CPT: 35480, 35481, 35482, 35483, 35485, 35490, 35491, 35492, 35493, 35495	0.36
	Thrombectomy, lower limbs	CPT: 35875, 35876, 35879, 35881, 35883, 35884, 35903	0.22
	Repair of blood vessel	ICD-9: 39.56, 39.57, 39.58	0.04
Lower extremity amputation	Amputation	ICD-9: 84.10, 84.12, 84.14, 84.15, 85.17, 84.3, 84.91 (84.11)[b]; CPT: 27590, 27591, 27592, 27594, 27596, 27599, 27880, 27881, 27882, 27888, 27889, 28800, 28805, 28810, 28820, 28825	2.12

(*Continued on next page*)

Supplementary Table (online only). Continued.

Category	*Diagnosis/procedure*	*Associated ICD-9 or CPT codes*	*Frequency of occurrence (%)*
	Chronic infection of amputation stump	ICD-9: (997.62)[b]	0.10
	Disarticulation	ICD-9: 84.13, 84.16, 84.18; CPT: 27295, 27598	0.03

[a]American Medical Association, Chicago, Ill.
[b]Must be accompanied by one of the following codes: 440.20, 440.21, 440.22, 440.23, 440.24.
[c]Must be accompanied by one of the following codes: 35556, 35566, 35571, 35583, 35585, 35587, 35623, 35656, 35666, 35671.