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Association of Opioid Use and Peripheral Arterial Disease

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Abstract

Two Sentences: Private insurance prescription records from 2007–2015 demonstrated nearly 25% of patients with PAD have high opioid use, defined as ≥2 opioid prescriptions in a given year. Patients undergoing treatment for PAD and those with a diagnosis of critical limb ischemia were at higher risk for high opioid utilization.

Table of Contents Summary: This retrospective study of the Truven Health Marketscan database of nearly 180,000 patients found 24.7% of patients with peripheral artery disease (PAD) meeting high opioid use criteria. Critical limb ischemia and treatment for PAD were associated with increased risk high opioid use.

Introduction: Prescription opioids account for 40% of all U.S. opioid overdose deaths, and national efforts have intensified to reduce opioid prescriptions. Little is known about the relationship between peripheral arterial disease (PAD) and high-risk opioid use. The objectives of this study were to evaluate this relationship and to assess the impact of PAD treatment on opiate usage.

Methods: In this retrospective cohort study, the Truven Health Marketscan database, a deidentified national private insurance claims database, was queried to identify patients with PAD (≥2 ICD-9 diagnoses codes of PAD ≥2 months apart, with at least 2 years of continuous enrollment) from 2007–2015. Critical limb ischemia (CLI) was defined as the presence of rest pain, ulcers or gangrene. The primary outcome was high opioid use, defined as ≥2 opioid prescriptions within a one-year period. Multi-variable analysis was used to determine risk factors for high opioid use.

Results: A total of 178,880 patients met the inclusion criteria, 35% of whom had CLI. Mean ± SD follow-up time was 5.3 ±2.1 years. An average of 24.7% of patients met the high opioid use criteria in any given calendar year, with a small but a significant decline in high opioid use after 2010 (P<0.01). During years of high opioid use, 5.9 ±5.5 yearly prescriptions were filled. A new diagnosis of PAD increased high opioid use (21.7% before diagnosis vs. 27.3% after diagnosis, P<0.001). A diagnosis of CLI was also associated with increased high opioid use (25.4% before

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diagnosis vs. 34.5% after diagnosis; P<0.001). Multi-variable analysis identified back pain (OR 1.89, 95% CI 1.84–1.93, P<0.001) and illicit drug use (OR 1.87, 95% CI 1.72–2.03, P<0.001) as the highest predictors of high opioid use. A diagnosis of CLI was also associated with higher risk (OR 1.61, 95% CI 1.57–1.64, P<0.001). A total of 43,443 PAD patients (24.3%) underwent 80,816 PAD related procedures. After excluding peri-procedural opioid prescriptions (4.9% of all opioid prescriptions), the yearly percentage of high opioid users increased from 25.8% pretreatment to 29.6% post-treatment (P<0.001).

Conclusion: Patients with PAD are at increased risk for high opioid use, with nearly one-quarter meeting described criteria. CLI and treatment for PAD additionally increase high opioid utilization. In addition to heightened awareness and active opioid management, our findings warrant further investigation into underlying causes and deterrents of high-risk opioid use.

Keywords

Peripheral Artery Disease; Opioids; percutaneous vascular intervention

Introduction

Opioid related deaths have continued to increase in the United States in recent years, and 40% of opioid related deaths in 2016 were due to prescription opioids.[1–3] Although previous studies have identified a number of high risk diagnoses associated with opioid use[4,5], little is known regarding the relationship between a diagnosis of peripheral arterial disease (PAD) and opioid use. As decreased perfusion can lead to ischemic pain (i.e. claudication and/or ischemic rest pain) and pain from non-healing wounds, health care professionals may prescribe opioid medications to help alleviate symptoms. However, prescribing opioids to treat chronic symptoms may lead to high opioid use, putting patients at risk for both opioid dependence and abuse.[5–7]

As the primary goal of open or percutaneous revascularization procedures is to alleviate pain by improving blood flow, successful intervention should in theory lead to decreased opioid use. Given the current lack of literature regarding opioid prescribing patterns in patients with PAD, the primary objectives of this study were two-fold: first, to evaluate the baseline relationship between PAD and opioid use and determine if PAD patients represent a high-risk cohort for high opiate use; and second, to assess whether treatment of PAD impacts opioid use.

Methods

The Truven Health Marketscan database, a de-identified, national private insurance claims database, was queried to identify patients from 2007–2015 with a diagnosis of PAD. This comprehensive database covers over 50% of the privately insured US population, but excludes patients with Medicare and Medicaid coverage.[8] Patients were determined to have PAD if they had ≥ 2 International Classification of Disease 9th edition (ICD-9) codes for PAD in the inpatient and/or outpatient claims records, ≥2 months apart.[9] Other inclusion criteria included ≥ 2 years of continuous enrollment and enrollment in an insurance plan that submits outpatient pharmaceutical claims, approximately 40–50% of enrollees.

Patients with PAD were identified using the following ICD-9 codes: 440.20, 440.21, 440.22, 440.23, 440.24, and 440.39. Patients with critical limb ischemia (CLI) were identified with ICD-9 codes 440.22, 440.23, and 440.24 corresponding to rest pain, ulcers or gangrene respectively; and/or lower extremity wound codes 707.1, 707.10, 707.11, 707.12, 707.13, 707.14, 707.15, and 707.19. We excluded patients with only a lower extremity wound code and no corresponding PAD code to eliminate patients with lower extremity wounds of non-vascular etiologies.

The primary outcome was high opioid use, defined as ≥2 opioid prescriptions within a one-year period, representing a definition used in previously published studies adapted to the study time frame.[10,11] Using the outpatient prescription file, opioid prescriptions were identified by the therapy class “60” classification. Prescriptions with cough/cold combination, opium, or suppository form were excluded, and prescriptions with a quantity less than 1 were also excluded. Prescriptions filled within 90 days of a PAD-related procedure, identified by CPT codes for lower extremity open/percutaneous revascularization or amputation (see Supplemental Table 1) were also excluded. CPT codes 37205–37208 recorded after Jan. 1, 2011 were not counted as a PAD-related procedure as these were replaced with more specific CPT codes that specified revascularization of the lower extremities.

Morphine equivalents (MEQ) were calculated using the outpatient pharmaceutical claims file in order to standardize dosing between opioid formulations. Prescription drug names, strengths, and quantities prescribed were noted and converted to MEQ according to a previously described conversion factor.[12]

The effect of a PAD diagnosis on high opioid use was investigated by comparing rates of high opioid use in the pre-diagnosis period with those in the post-diagnosis period; high opioid years prior to the first diagnosis of PAD were compared to high opioid years after the diagnosis. Patients with PAD diagnoses were also stratified by CLI status and CLI patients were analyzed for high opiate use criteria as a separate subgroup. A subgroup of patients who underwent PAD related procedures were also analyzed and compared to those who did not undergo revascularization procedures. This analysis was also separately performed for CLI patients.

Patient demographics were obtained from member enrollment data and comorbidities were assessed using both outpatient and inpatient medical claims files. We evaluated comorbidities using the Charlson Comorbidity index.[13] We also specifically evaluated the presence of diagnoses previously associated with opioid use (Supplemental Table 2).[4,14] Patients were classified into an urban setting if they resided in a metropolitan statistical area and categorized by region: Northeast, North Central, South, West, and unknown. Descriptive statistics were used to compare patients meeting high opioid use criteria during any year of follow-up with those who did not. Multivariable analysis was then performed to determine factors associated with high opioid use while adjusting for known confounders. Odds ratios (OR) are reported with 95% confidence intervals (95% CI). Averages are expressed as mean ± standard deviation unless otherwise specified. Data cleaning was performed using SAS Enterprise Guide (Cary, NC), and statistical analysis was performed using Stata v14

(College Station, TX). The Stanford University Institutional Review Board determined that this project did not meet the definition of human subjects research and exempted it from further review. This study was approved by the Stanford IRB and patient consent was waived as the database was deidentified.

Results

A total of 178,880 PAD patients met inclusion criteria, with a mean follow-up time of 5.3±2.1 years. 63,400 patients (35%) had a diagnosis of CLI. Among PAD patients without CLI, 20,799 (18.0%) underwent a PAD-related procedure. For patients with CLI, 23,317 (36.8%) underwent a PAD-related procedure (Figure 1). After excluding opioid prescriptions within 90-days of a PAD-related procedure, of the 950,355 patient-years evaluated, 234,118 (24.7%) met high opioid use criteria

The number of patients meeting high opioid use criteria increased from 2007–2010; peaking in 2010 and then declining until 2015. This trend was statistically significant ($p<0.01$, see Figure 2a). The distribution of MEQ per patient by calendar year follows a right skewed distribution (Figure 2b), with the median MEQ ranging from 600–900 and high end users receiving approximately 10,000 MEQ per year. Patients received an average of 5.9±5.5 opioid prescriptions per year when meeting high opioid use criteria.

Patient demographics and comorbidities stratified by high opioid use are noted in Table 1. High opioid users were slightly younger and more likely to be female. Patients meeting high opioid use criteria also had more comorbidities, as noted by a higher Charlson score. Other previously described risk factors for opioid use were more common in PAD patients with high opioid use, including arthritis, pain syndromes, depression, and substance use disorders. A diagnosis of CLI was more prevalent among patients in the high opioid use group. A diagnosis of chronic pain was found in 2.7% of patients not meeting high opioid use criteria and in 18.8% of patients meeting high opioid use criteria ($P<0.001$).

Multivariable regression analysis identified dementia as the only co-morbidity associated with a lower risk of high opioid use (OR 0.77, 95% CI 0.70–0.86, $P<0.001$). With the exception of cerebrovascular disease, hemiplegia/ paraplegia, and AIDS, the remaining chronic conditions were associated with an increased risk of high opioid use. Previously described high risk conditions were also associated with high opioid use with back pain (OR 1.89, 95% CI 1.85–1.94, $P<0.001$) and illicit drug use (OR 1.89, 95% CI 1.73–2.06, $P<0.001$) having the highest risk for high opioid use. CLI was also independently associated with a higher risk of high opioid use (OR 1.62, 95% CI 1.58 – 1.67, $P<0.001$), similar to a diagnosis of osteoarthritis or tobacco use, see Table 2. Patients living in an urban setting (OR 0.91, 95% CI 0.88–0.93, $P<.001$) and patients living in the Northeast region (OR 0.64, 95% CI 0.59 – 0.69, $P<.001$) were associated with decreased risk of meeting high opioid use criteria.

Analysis of the relationship between a PAD diagnosis and high opioid use demonstrated that rates of high opioid use increased from 21.7% in years prior to diagnosis with PAD to 27.3% in the years following diagnosis, an absolute increase of 5.6% (Figure 3a). High opioid use

increased from 19.8% to 23.0% for patients without CLI and from 25.4% to 35.5% for patients with CLI, an absolute difference of 9.1%.

Treatment for PAD was found to increase rates of high opioid use, even when peri-procedural opioid prescriptions were excluded. High opioid use increased from 25.8% in years prior to treatment to 29.6% in years following treatment (Figure 3b). For patients without CLI, high opioid use years increased from 22.7% prior to treatment to 25.9% after treatment, whereas high opioid use increased from 30.8% prior to treatment to 37.1% after treatment for patients with CLI. For patients who did not undergo a PAD related procedure the overall rate of high opioid users was 24.3%, (21.6% for patients with no CLI and 32.6% for patients with CLI).

A total of 80,816 PAD-related procedures were performed in 43,443 patients. The median time from diagnosis to the first PAD-related procedure was 81 days (interquartile range 26–367). Fifty-six percent of PAD procedures resulted in an opioid prescription within 90 days following the procedure. This percentage was the highest for open revascularization (82.7%), followed by above ankle amputation (72.5%) and percutaneous revascularization (44.6%) (Table 3). A total of 105,155 opioid prescriptions were prescribed within 90-days of PAD related treatments and these were not counted towards the high opioid use criteria. These treatment-related opioids accounted for only 4.9% of the 2,153,169 opioid prescriptions for all patients during follow-up.

Discussion

Opiate use is highly prevalent among patients with PAD, and to our knowledge this study is the first to describe opioid prescription patterns in patients with PAD. An average of 24.7% of PAD patients met criteria for high use opioid use, after excluding PAD treatment related prescriptions. Our study found that a new diagnosis of PAD increases high opioid use percentage from 21.7% to 27.3%, and this increase was even greater for patients with a new diagnosis of CLI (25.4% to 35.5%). A diagnosis of CLI was independently associated with an increased risk of high opioid use (OR 1.61). We additionally demonstrated that PAD treatment is associated with an increase in high opioid use, as the percentage of patients meeting criteria increased from 26% pre-treatment to 30% post treatment, despite censoring peri-procedural prescriptions. This finding should alarm physicians to evaluate their own opioid prescribing patterns after PAD interventions to decrease the risk for long term use.

Although PAD patients often have multiple other comorbidities contributing to pain and increased risk of receiving opioid prescriptions, this article highlights that PAD patients are frequently prescribed opioids, especially patients with CLI and those who undergo PAD-related treatment. PAD itself can cause pain, as decreased blood supply to the lower extremities may trigger increased pain through nociception, ischemia, and neuropathy.[15] Patients may also have phantom limb pain, which may persist after major amputation. Although the primary goal of revascularization is often to improve blood supply in order alleviate symptoms (especially when not performed for limb salvage), we found that high opioid use actually increased after PAD interventions. This may suggest that opioid prescriptions following PAD intervention may result in opioid dependence and long-term

use, highlighting the importance of judicious perioperative prescribing practices. Chronic opioid use has been shown to increase after both minor and major surgical procedures and has been implicated as one of the many contributors to the overall opioid epidemic and the availability of prescriptions opioids to the US population.[10,16] Clinicians should therefore be cautious when prescribing opioids for patients with PAD, especially when multiple co-morbidities are present.

Our study found that 56.0% of PAD related procedures have an opioid prescription within 90 days of the procedure. Further investigation is warranted to determine individual prescribing patterns after PAD interventions (e.g. endovascular versus open revascularization), and to determine the risks of chronic opioid use especially in opioid naïve patients. As our results mirror national trends of decreasing rate of overall opioid prescriptions since 2010 (see Figure 2a), longer duration of opioid prescription (e.g. higher quantity of pills) rather than the quantity of opioid prescriptions may be contributing to the opioid epidemic.[17] Current efforts by the Michigan Surgical Quality Collaborative have set opioid prescribing recommendations after common general surgery procedures[18] after a growing body of data has suggested that surgical patients are often prescribed more pills than they use.[19] Similar efforts for common vascular procedures may lead to decreased opioid prescriptions for patients with PAD and CLI. As increased opioid exposure is associated with increased arterial stiffness and increased vascular age[20], health care providers should particularly minimize opioid prescriptions in patients with PAD.

This study has several limitations inherent to research using insurance claims data. This dataset is unable to link opioid prescriptions to a specific diagnosis, and prescriptions within 90 days of a PAD procedure may have been issued due to other comorbidities or non-PAD surgical interventions. The database contains limited information regarding type of physician practice, and physician identification was not readily available for all prescription records. As the majority of patients hold private insurance prior to Medicare eligibility there is also limited generalizability to patients above 65 years of age and those with government sponsored insurance. Finally, minor procedures, including toe amputations and wound debridements, were not analyzed and may have contributed to an increase in opioid prescriptions for patients with CLI.

Conclusions

Patients with PAD are at risk for high opioid use, and patients with CLI and those undergoing treatment for PAD appear to be at even greater risk. In addition to heightened awareness and active opioid management, our findings warrant further investigation into the underlying causes of this, as well as methods to deter high-risk opioid use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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Article Highlights:

Type of Research: Retrospective study of the Truven Health Marketscan, a national private insurance claims database.

Key findings:

Analysis of nearly 180,000 patients found 24.7% of patients with peripheral artery disease (PAD) meeting high opioid use criteria from 2007–2015. A diagnosis of critical limb ischemia (CLI) increased high opioid use to 34.5% and treatment for PAD increased high opioid use to 29.6%, even after censoring prescriptions within 90 days of the procedure.

Take home message:

Nearly a quarter of patients with PAD meet the high opioid use criteria in a given year, and CLI and treatment for PAD increases the risk of high opioid use.

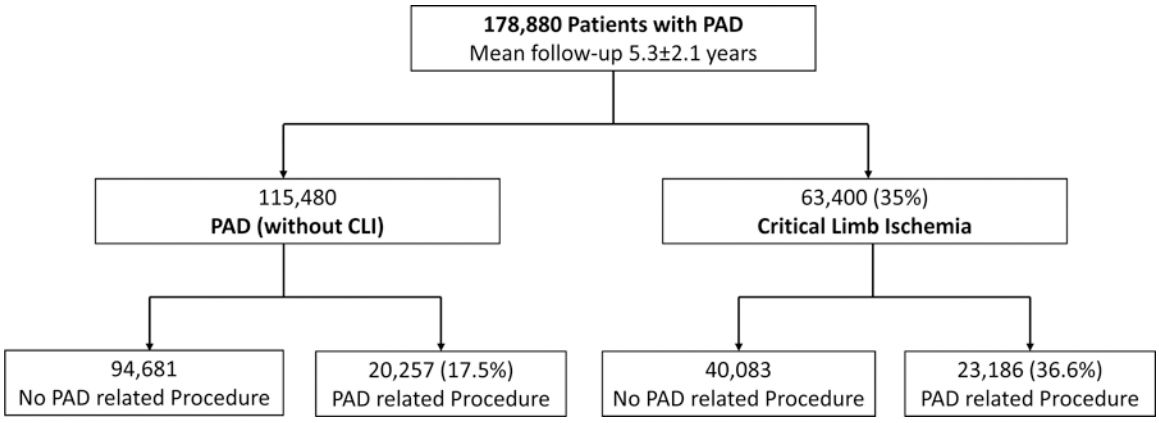

Figure 1.
Number of patients meeting high opioid use criteria by year

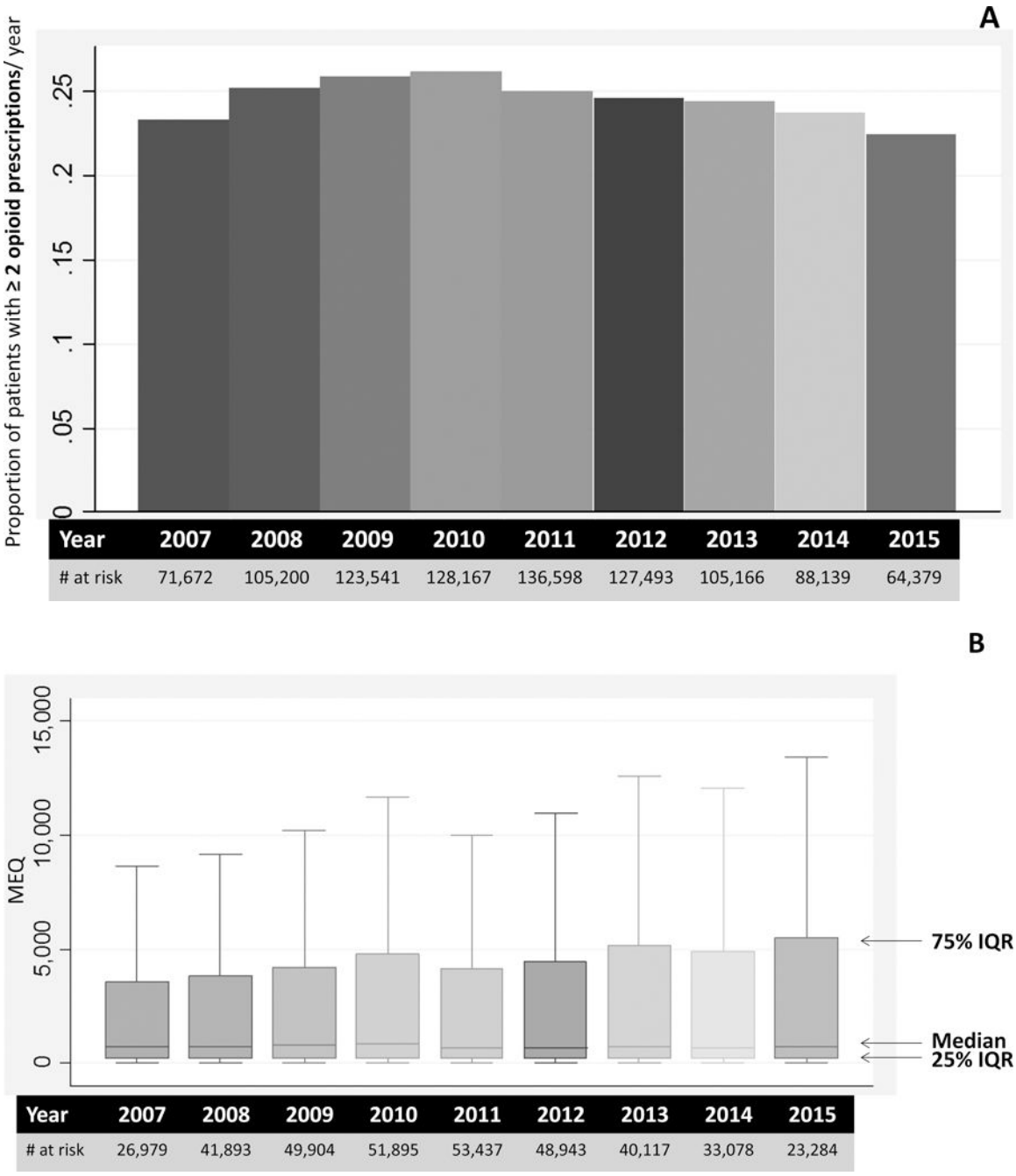

Figure 2a.

PAD patients meeting high opioid use criteria of ≥2 opioid prescriptions in a given year by year. **2b.** Box and Whisker's Plot of morphine equivalents (MEQ) per patient by year, IQR - interquartile range.

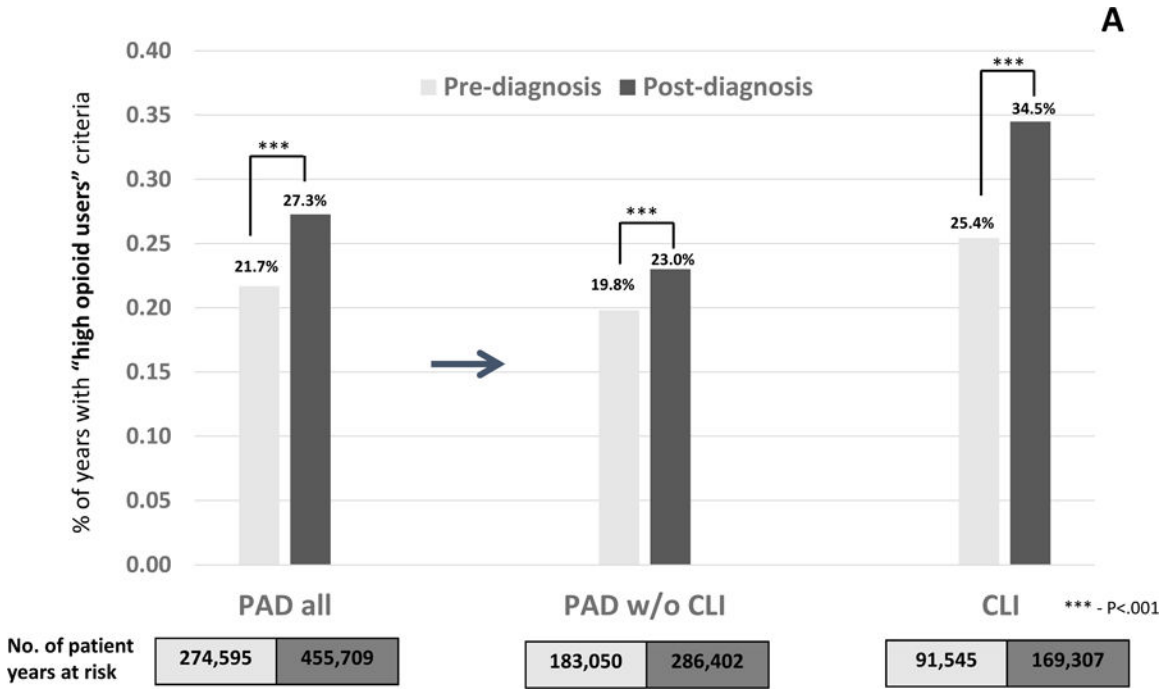

Figure 3a.
Relationship of diagnosis and high use - all patients, PAD without CLI, and CLI

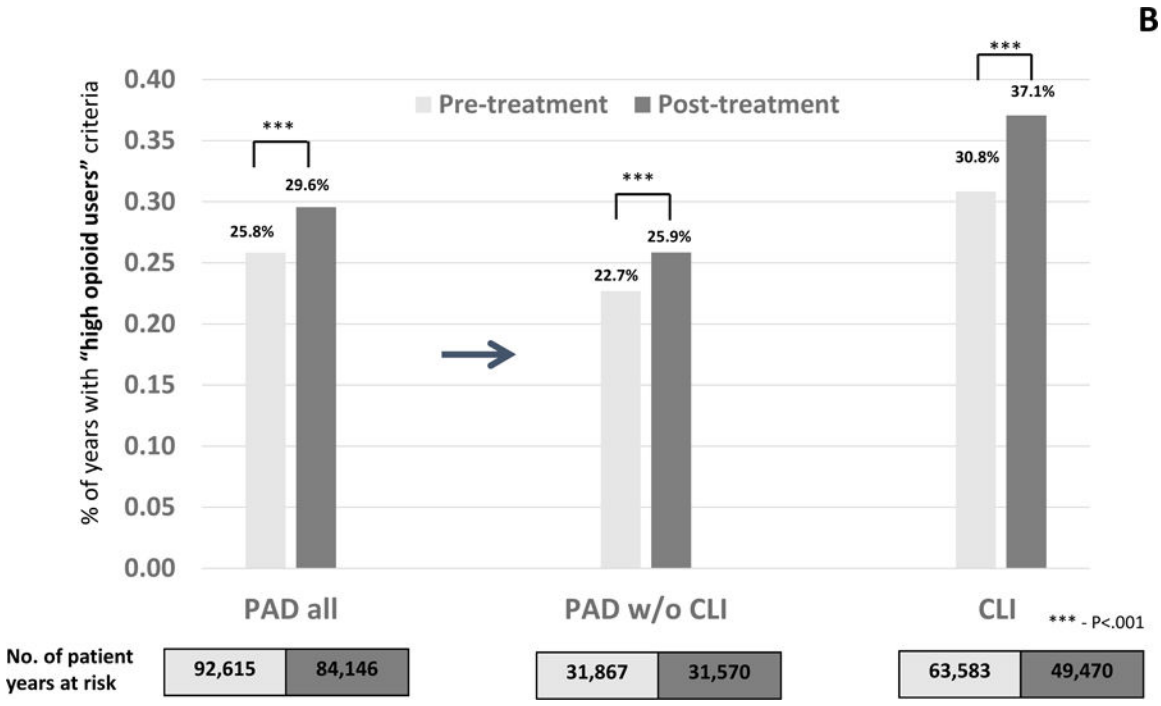

Figure 3b.

Relationship of treatment and high opioid use - all patients, PAD without CLI, and CLI

Table 1.

Comparisons of patient demographics and co-morbidities for those who did and did not meet high opioid use criteria during follow-up.

	Patients w/o high opioid use criteria (n=87,889)	Patients with high opioid use criteria (n=90,991)	Absolute Difference	P-Value
Age	53.5 ± 7.7	53.0 ± 7.1	−0.6	<.001
Female Gender	36,286 (41.3%)	40,706 (44.7%)	3.4%	<.001
Charlson Index	4.0 ± 2.6	5.3 ± 3.2	1.3	<.001
Myocardial infarction	10,778 (12.3%)	16,742 (18.4%)	6.1%	<.001
Congestive heart failure	16,274 (18.5%)	26,099 (28.7%)	10.2%	<.001
Peripheral vascular disease	87,889 (100%)	90,991 (100%)	-	--
Cerebrovascular disease	33,245 (37.9%)	39,266 (43.1%)	5.2%	<.001
Dementia	870 (1.0%)	1,237 (1.4%)	0.4%	<.001
Chronic pulmonary disease	30,127 (34.3%)	45,737 (50.2%)	15.9%	<.001
Rheumatologic disease	4,890 (5.6%)	9,339 (10.3%)	4.7%	<.001
Peptic ulcer disease	3,310 (3.8%)	6,067 (6.7%)	2.9%	<.001
Mild liver disease	11,425 (13.0%)	17,918 (19.7%)	6.7%	<.001
Diabetes	44,875 (51.1%)	53,000 (58.2%)	7.1%	<.001
Diabetes with chronic complications	24,525 (27.9%)	32,913 (36.2%)	8.3%	<.001
Hemiplegia or paraplegia	2,456 (2.8%)	4,280 (4.7%)	1.9%	<.001
Renal disease	12,612 (14.4%)	20,682 (22.7%)	8.3%	<.001
Any malignancy	9,243 (10.5%)	15,182 (16.7%)	6.2%	<.001
Moderate or severe liver disease	739 (0.8%)	1,746 (1.9%)	0.9%	<.001
Metastatic solid tumor	1,224 (1.4%)	3,888 (4.3%)	2.9%	<.001
AIDS	438 (0.5%)	562 (0.6%)	0.1%	<.001
Osteoarthritis	24,969 (28.4%)	45,085 (49.5%)	21.1%	<.001
Joint Pain	42,016 (47.8%)	65,127 (71.5%)	23.7%	<.001
Rheumatoid Arthritis	3,110 (3.5%)	6,256 (6.9%)	3.4%	<.001
Migraine	3,867 (4.4%)	8,154 (9.0%)	4.6%	<.001
Abdominal Pain	33,050 (37.6%)	50,642 (55.6%)	18.0%	<.001
Back Pain	34,122 (38.9%)	58,572 (64.3%)	25.4%	<.001
Neck Pain	17,465 (19.9%)	31,971 (35.1%)	15.2%	<.001
Tobacco Use	24,353 (27.7%)	36,044 (39.6%)	11.9%	<.001
Alcohol Use	3,095 (3.5%)	5,684 (6.2%)	2.7%	<.001
Illicit Drug Use	819 (0.9%)	3,397 (3.7%)	2.8%	<.001
Depression	13,914 (15.8%)	29,037 (31.9%)	16.1%	<.001
Critical Limb Ischemia	25,388 (28.9%)	38,012 (41.8%)	12.9%	<.001
Urban	74,729 (85.1%)	74,777 (82.1%)	−2.9%	<.001
Region				
Northeast	26,925 (30.6%)	17,365 (19.1%)	−11.6	<.001
North Central	18,018 (20.5%)	22,895 (25.2%)	−4.6%	
South	32,678 (37.2%)	39,350 (43.2%)	6.0%	
West	8,600 (9.8%)	9,789 (10.7%)	1.0%	

	Patients w/o high opioid use criteria (n=87,889)	Patients with high opioid use criteria (n=90,991)	Absolute Difference	P-Value
Unknown	1,618 (1.8%)	1,642 (1.8%)	<.1%	

Table 2.

Multi-variable analysis of risk factors for high opioid use.

	Odds Ratio	95% Confidence Interval	P-Value
Age (per 1 year increase)	0.99	0.99–0.99	<.001
Female Gender	0.90	0.88–0.92	<.001
Charlson Index			
Myocardial infarction	1.25	1.21–1.29	<.001
Congestive heart failure	1.23	1.20–1.27	<.001
Peripheral vascular disease	1	-	-
Cerebrovascular disease	1.02	1.00–1.04	.08
Dementia	0.77	0.70–0.86	<.001
Chronic pulmonary disease	1.31	1.28–1.34	<.001
Rheumatologic disease	1.20	1.12–1.28	<.001
Peptic ulcer disease	1.14	1.08–1.20	<.001
Mild liver disease	1.05	1.02–1.08	.001
Diabetes	1.06	1.04–1.09	<.001
Diabetes with chronic complications	1.05	1.04–1.07	<.001
Hemiplegia or paraplegia	1.03	1.00–1.06	.052
Renal disease	1.11	1.09–1.13	<.001
Any malignancy	1.14	1.13–1.17	<.001
Moderate or severe liver disease	1.07	1.04–1.11	<.001
Metastatic solid tumor	1.15	1.14–1.17	<.001
AIDS	1.00	0.98–1.03	.52
Osteoarthritis	1.65	1.61–1.69	<.001
Joint Pain	1.65	1.61–1.69	<.001
Rheumatoid Arthritis	1.06	0.98–1.15	.16
Migraine	1.37	1.31–1.43	<.001
Abdominal Pain	1.33	1.31–1.37	<.001
Back Pain	1.89	1.85–1.94	<.001
Neck Pain	1.28	1.25–1.31	<.001
Tobacco Use	1.54	1.51–1.58	<.001
Alcohol Use	1.18	1.12–1.24	<.001
Illicit Drug Use	1.89	1.73–2.06	<.001
Depression	1.59	1.55–1.63	<.001
Critical Limb Ischemia	1.62	1.58–1.67	<.001
Urban vs. Rural	0.91	0.88–0.93	<.001
Region compared to Unknown			
Northeast	0.64	0.59–0.69	<.001
North Central	1.29	1.19–1.40	<.001
South	1.32	1.22–1.43	<.001
West	1.20	1.11–1.31	<.001

Table 3.

Percentage of procedures with opioid prescriptions within 90 days of the procedure.

	Number	Procedures with opioid Rx within 90 days	Percentage
Total Procedures *	80,816	45,322	56.0%
Percutaneous Revascularization	48,798	21,745	44.6%
Open Revascularization	6,732	5,565	82.7%
Above Ankle Amputation	30,510	22,129	72.5%

* Based on procedure dates, patients may have more than 1 type of procedure on a given date