ORIGINAL RESEARCH

Underutilization of Evidence-Based Smoking Cessation Support Strategies Despite High Smoking Addiction Burden in Peripheral Artery Disease Specialty Care: Insights from the International PORTRAIT Registry

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Background—Smoking is the most important risk factor for peripheral artery disease (PAD). Smoking cessation is key in PAD management. We aimed to examine smoking rates and smoking cessation interventions offered to patients with PAD consulting a vascular specialty clinic; and assess changes in smoking behavior over the year following initial visit.

Methods and Results—A total of 1272 patients with PAD and new or worsening claudication were enrolled at 16 vascular specialty clinics (2011–2015, PORTRAIT (Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories) registry). Interviews collected smoking status and cessation interventions at baseline, 3, 6, and 12 months. Among smokers, transition state models analyzed smoking transitions at each time point and identified factors associated with quitting and relapse. On presentation, 474 (37.3%) patients were active, 660 (51.9%) former, and 138 (10.8%) never smokers. Among active smokers, only 16% were referred to cessation counseling and 11% were prescribed pharmacologic treatment. At 3 months, the probability of quitting smoking was 21%; among those continuing to smoke at 3 months, the probability of quitting during the next 9 months varied between 11% and 12% ($P<0.001$). The probability of relapse among initial quitters was 36%. At 12 months, 72% of all smokers continued to smoke.

Conclusions—More than one third of patients with claudication consulting a PAD provider are active smokers and few received evidence-based cessation interventions. Patients appear to be most likely to quit early in their treatment course, but many quickly relapse and 72% of all patients smoking at baseline are still smoking at 12 months. Better strategies are needed to provide continuous cessation support.

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Key Words: peripheral arterial disease • smoking

Peripheral artery disease (PAD) affects 202 million adults worldwide and is associated with significant morbidity and mortality.[1] Cigarette smoking is the most important and modifiable risk factor for PAD. Patients with PAD who smoke have higher rates of disease progression,[2–4] greater risk of complications secondary to PAD,[5] poor post-procedural outcomes,[6] compromised functional status,[7] and increased hospitalizations; all accounting for a higher patient and societal burden.[8] Furthermore, active tobacco use in patients with PAD is strongly associated with a significant increase in

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Accompanying Tables S1 through S4 and Figures S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010076

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Clinical Perspective

What Is New?

- A third of 1272 patients with symptomatic peripheral arterial disease were active smokers on initial presentation to a vascular clinic, however <1 in 5 were referred to formal cessation counseling and 1 in 10 were prescribed pharmacologic treatment to help stop smoking.
- Chances for quitting were highest in the first 3 months (20%), although about a third of these initial quitters relapsed within a year, with 72% of active smokers at baseline continuing to smoke a year later.

What Are the Clinical Implications?

- The dynamic nature of peripheral artery disease patient's smoking practices underscores the need for ongoing assessment of smoking, even among those who report that they had quit.
- Improved efforts to offer ongoing evidence-based cessation support are needed for patients with peripheral artery disease.

cardiovascular events, including myocardial infarction and death,[5,9–11] underscoring the urgent need for smoking cessation efforts in this population.

Smoking cessation is a critical component of secondary prevention guidelines in PAD and has been endorsed as a performance measure of quality.[12] In fact, the guidelines for PAD management give a grade IA recommendation for asking the smoking status of a PAD patient at each assessment and offering smoking cessation support to all who actively smoke.[13] Despite the key role that has been attributed to smoking as a risk factor in PAD, and the availability of effective smoking cessation treatments,[13–15] there are surprisingly few contemporary data describing the current prevalence of smoking in PAD patients and physicians' efforts to encourage smoking cessation.[16–18] There is also limited understanding how the habits of smokers with PAD change after they consult their physician for symptoms related to PAD.

To address these gaps in knowledge, we used the PORTRAIT (Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories) registry, an international, multicenter registry of patients presenting to specialty clinics with new or worsening symptoms of PAD, to assess the smoking status of patients with PAD. The PORTRAIT registry is an ideal foundation for evaluating smoking cessation interventions at critical time in PAD care, as enrolled patients had new or worsening PAD symptoms warranting specialty consultation. Therefore, we aimed to: (1) examine smoking rates in patients with PAD consulting a vascular specialty clinic; (2) determine smoking cessation interventions provided at those visits and its variability across centers; and (3) assess changes in smoking behavior over the year following initial PAD consultation. Also, as the PORTRAIT registry enrolled patients from the United States, the Netherlands, and Australia, we examined differences in smoking patterns and provision of smoking cessation support across these countries.

Methods

Because of the sensitive nature of the data collected for this study, requests to access a de-identified data set from qualified researchers trained in human subject confidentiality protocols may be considered on an individual basis by contacting the PORTRAIT group on the website.[19]

Study Population

PORTRAIT is a multicenter, international prospective registry that enrolled 1275 patients with symptomatic PAD presenting to 16 PAD specialty clinics across the United States, the Netherlands, and Australia from June 2011 to December 2015. Study details have been described previously.[20] In brief, adults presenting to a PAD specialist with new-onset or a recent exacerbation of exertional leg symptoms, and an abnormal resting ankle brachial index (≤0.90) or a significant drop in post-exercise ankle pressure of ≥20 mm Hg, were included. Patients with non-compressible ankle brachial indexes (≥1.3), critical limb ischemia, prior peripheral intervention within the past year on the same leg with current claudication symptoms and those who were incarcerated, hard of hearing, unable to speak English, Dutch, or Spanish or unable to provide informed consent were excluded.

Initial visit in this registry refers to the first visit for patients with PAD with a specialty PAD provider for evaluation of their claudication symptoms. Patient demographics, health status, psychosocial characteristics, and socioeconomic and cardiovascular lifestyle factors were obtained by interview at the initial visit. Patients' symptoms, medical history, comorbidities, and PAD diagnostic information were abstracted from their medical records. Serial information about patients' health status, psychosocial and lifestyle factors, including smoking status, was collected at 3, 6, and 12 months of follow-up through telephone interviews.

All study participants provided either written or telephonic informed consent. The study protocol was approved by Institutional Review Boards of all participating sites.

Smoking Status Assessment

Baseline smoking status was assessed through in-person interviews using the following response options[21]: (1) I have

never smoked, not even a puff, (2) I have smoked in the past but <100 cigarettes in total, (3) I stopped smoking >1 year ago, (4) I stopped smoking between 1 month and 1 year ago, and (5) I have smoked (even a puff) in the past 30 days. Responses (1) and (2) were categorized as never smokers, responses (3) and (4) were categorized as former smokers, and response (5) was categorized as current smokers. At follow-up assessments, patients were asked via telephone interviews if they had smoked within the past 30 days (regardless of their baseline smoking status).

Provision of Smoking Cessation Support

The smoking cessation intervention performance measure was collected at baseline via chart abstraction and confirmed with patient interviews. It included 3 metrics: (1) physician advice to quit smoking; (2) referral to formal smoking cessation counseling; and (3) prescription of pharmacologic treatment (bupropion or varenicline) or nicotine replacement therapies (nicotine patch, gum, lozenge, nasal spray, or inhaler) to aid smoking cessation. For patients who did not receive smoking cessation support, patient (eg, patient refusal), medical (eg, medical contra-indication or prior receipt of treatment), and system (eg, unavailability of smoking cessation program within the medical system, insurance issues, etc,). were captured if they were felt to be contributory.

Statistical Analysis

Smoking status at initial visit

The proportion of current, former, and never smokers at the initial visit was calculated. Differences between demographic, socioeconomic, psychosocial, risk factors, health status, treatment, and disease characteristics were compared among patients by smoking status using ANOVA for continuous variables and the Chi-square or Fisher exact test for categorical variables.

Provision of smoking cessation support

Rates of provision of overall and individual components of smoking cessation support measures were assessed for the entire population.

Variability in provision of smoking cessation support

Variability in provision of smoking cessation support measures among sites was assessed by estimating median odds ratios (MORs). It estimates the average relative difference in provision of cessation support between 2 randomly selected sites. An MOR of 1 for site variability indicates no site-level variation in offering cessation support, while an MOR of 2 suggests a median 2-fold difference in the odds of receiving cessation support between 2 random sites. As all smoking patients should receive cessation support regardless of their personal characteristics, we did not adjust for patient factors in the MOR model. We however, did adjust for country and provider to assess the effect of country and provider on site variability.

Predominant smoking patterns in active smokers over the course of a year

Using both baseline and follow-up smoking status information, proportions of patients who smoked throughout the follow-up period (persistent smokers), stopped smoking and did not restart on follow-up (sustained quitters), and those who stopped smoking but started smoking on follow-up (relapsers) were estimated among active smokers at baseline.

Transition probabilities between smoking and non-smoking states on follow-up

Recognizing that smoking cessation is a dynamic process where different patients quit and relapse at and for various times over the period of observation, we fit a transition model to estimate the probabilities of transitioning from a smoking to non-smoking state (quit attempts) and from a non-smoking state to a smoking state (relapse) between consecutive assessments. Based on the framework developed by Yeh et al,[22] we used a time-inhomogeneous non-Markov transition model to identify potential patient factors associated with transitions from smoking to non-smoking (quit) and from non-smoking to smoking (relapse). The transition model consisted of 2 simultaneous longitudinal logistic regressions, 1 predicting quit attempts and 1 predicting relapses. Generalized estimating equations were used to account for within-patient correlations between repeated assessments. Prespecified predictors at baseline included country, age, sex, non-Caucasian race, marital status, education, chronic lung disease, positive screen for alcohol abuse (Alcohol Use Disorders Identification Test-Concise [AUDIT-C] questionnaire),[23] perceived stress score (Perceived Stress Scale-4),[24] patient health questionnaire-8 depression score,[25] positive screen for anxiety (Generalized Anxiety Disorder-2 item scale [GAD-2]),[26] provision of smoking cessation supports at the time of the visit, smoking behavior transitions at 6 and 12 months, and patients' 3-month smoking status.

Missing data

Multiple imputation was used to account for missing smoking status information at follow-up assessments (14% [539/3816] of total time points), accounting for sociodemographic, comorbidity, psychosocial factors, smoking cessation measures, and smoking status at other available time points (listed in Table S1). Point estimates for smoking statuses, transition probabilities and model effects were similar for complete-case (Figure S1) and imputed data; we report results based on imputed data here, which correctly accounts for

Table. Baseline Characteristics of the Study Population, According to Smoking Status at Initial Visit

Characteristic	Current Smoker (n=474) (37.3%)	Former Smoker (n=660) (51.9%)	Never Smoker (n=138) (10.8%)	*P* Value
Demographics				
Age, y (mean±SD)	63.3±8.9	69.5±8.6	73.5±8.9	<0.001
Male sex	293 (61.8)	443 (67.1)	56 (40.6)	<0.001
Race				
White	377 (79.5)	556 (84.2)	111 (80.4)	0.11
Hispanic or Latino Ethnicity	5 (1.8)	11 (2.2)	0 (0.0)	0.34
Married	251 (53.4)	426 (64.6)	75 (54.7)	<0.001
Currently work for pay				
No	336 (71.0)	516 (78.5)	114 (83.2)	<0.001
Yes, full-time	95 (20.1)	76 (11.6)	15 (10.9)	
Yes, part-time	42 (8.9)	65 (9.9)	8 (5.8)	
Socioeconomic status				
Insurance	469 (98.9)	658 (99.7)	137 (99.3)	0.23
Education high school	286 (60.7)	486 (74.1)	100 (73.5)	<0.001
Finances end of month				
Some money left over	225 (48.9)	386 (60.1)	72 (52.6)	<0.001
Just enough to make ends meet	168 (36.5)	206 (32.1)	49 (35.8)	
Not enough to make ends meet	67 (14.6)	50 (7.8)	16 (11.7)	
Avoid care because of cost	84 (17.8)	80 (12.2)	14 (10.1)	0.01
Social support				
ESSI social support score (mean±SD)	21.7±5.0	22.4±4.3	21.6±4.7	0.02
PAD characteristics				
Ankle brachial index (mean±SD)	0.6±0.2	0.7±0.2	0.7±0.2	0.001
Symptom presentation				
Typical	373 (87.1)	532 (86.6)	104 (78.2)	
Atypical	55 (12.9)	82 (13.4)	29 (21.8)	0.03
Symptom onset				
New-onset	289 (61.0)	312 (47.3)	64 (46.4)	<0.001
Exacerbation	185 (39.0)	348 (52.7)	74 (53.6)	
Function: Rutherford category				
Mild claudication	101 (21.7)	150 (23.0)	34 (25.0)	0.80
Moderate claudication	233 (50.1)	325 (49.9)	61 (44.9)	
Severe claudication	131 (28.2)	176 (27.0)	41 (30.1)	
Laterality				
Unilateral	246 (51.9)	320 (48.5)	60 (43.5)	0.19
Bilateral	228 (48.1)	340 (51.5)	78 (56.5)	

Continued

Table. Continued

Characteristic	Current Smoker (n=474) (37.3%)	Former Smoker (n=660) (51.9%)	Never Smoker (n=138) (10.8%)	*P* Value
Lesion site				
Proximal	145 (30.7)	183 (28.0)	31 (22.8)	0.003
Distal	119 (25.2)	199 (30.4)	58 (42.6)	
Both	208 (44.1)	272 (41.6)	47 (34.6)	
Duration of pain				
<1 mo	15 (3.8)	13 (2.3)	2 (1.6)	0.39
1 to 6 mo	122 (31.2)	173 (30.0)	32 (26.2)	
7 to 12 mo	73 (18.7)	93 (16.1)	24 (19.7)	
>12 mo	181 (46.3)	298 (51.6)	64 (52.5)	
Vascular history				
Non-healing ulcer	3 (0.6)	6 (0.9)	7 (5.1)	0.001
Amputation	4 (0.8)	11 (1.7)	1 (0.7)	0.51
Peripheral vascular intervention	108 (22.8)	212 (32.1)	30 (21.7)	<0.001
Cardiovascular history				
Congestive heart failure	32 (6.8)	81 (12.3)	14 (10.1)	0.01
Dyslipidemia	353 (74.5)	542 (82.1)	117 (84.8)	0.001
Hypertension	331 (69.8)	562 (85.2)	123 (89.1)	<0.001
Cerebrovascular accident	61 (12.9)	69 (10.5)	16 (11.6)	0.45
Coronary artery disease	166 (35.0)	333 (50.5)	64 (46.4)	<0.001
Non-cardiac history				
Chronic kidney disease	34 (7.2)	86 (13.0)	23 (16.7)	<0.001
Chronic lung disease	98 (20.7)	119 (18.0)	3 (2.2)	<0.001
Sleep apnea	28 (5.9)	64 (9.7)	11 (8.0)	0.07
Depression requiring treatment	72 (15.2)	65 (9.8)	19 (13.8)	0.02
Diabetes mellitus	125 (26.4)	243 (36.8)	54 (39.1)	<0.001
Health status (mean±SD)				
Peripheral artery questionnaire (PAQ)				
Physical limitation	38.3±27.5	38.7±26.0	38.7±24.4	0.96
Symptom stability	42.8±22.3	43.8±20.1	42.0±21.8	0.58
Symptoms	42.8±23.3	44.8±22.2	43.0±24.0	0.28
Treatment satisfaction	83.6±21.4	83.1±20.7	81.7±21.6	0.65
Quality of life	48.2±26.7	51.3±25.1	54.3±26.8	0.03
Social limitation	61.1±31.5	64.3±29.5	64.7±28.4	0.18
Summary score	47.5±23.0	50.0±21.0	50.5±21.5	0.13
EQ5D: Score your health today	63.6±19.9	68.0±18.5	66.6±19.7	<0.001
PHQ-8 depression score	5.5±5.6	4.2±4.6	4.7±4.8	<0.001

Numbers are provided in n (%), unless otherwise indicated. ENRICHD indicates Enhancing Recovery in Coronary Heart Disease; EQ5D, EuroQOL-5 Dimensions; ESSI, ENRICHD Social Support Inventory; PAQ, peripheral artery questionnaire; PHQ-8, patient health questionnaire-8.

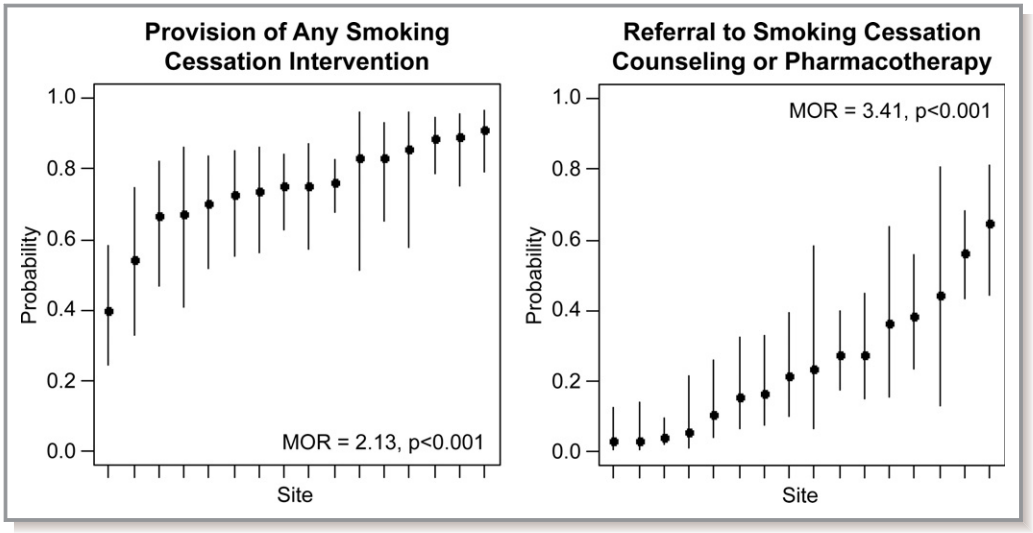

Figure 1. Site variability in provision of smoking cessation interventions. Median odds ratios estimate the median of all possible odds ratios between 2 randomly selected sites, MOR of 1 suggests no variability (unadjusted analysis). MOR indicates median odds ratio.

biases attributable to observed factors and uncertainty because of missingness.

Country-specific smoking and smoking cessation patterns

Country-specific differences between patients in the United States, the Netherlands, and Australia in smoking behavior at baseline, change in smoking patterns on follow-up, and provider adherence to smoking cessation measures were compared using Chi-square test or Fisher-exact test.

All analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC) and R version 3.3.1.[27]

Results

Smoking Status at Initial Visit

Of 1272 patients presenting with PAD-related symptoms to a vascular specialty clinic, 474 (37.3%) patients were active, 660 (51.9%) former (585 quit >1 year ago, 75 quit between 1 month–1 year), and 138 (10.8%) were never smokers at the initial visit. Current smokers at the initial visit were younger, more likely to be working either full-time or part-time and less likely to have a high school or greater education (Table). They also were more likely to present with new-onset symptoms that were longer in duration and to have lower ankle brachial indexes. They were more likely to have proximal disease and have had a prior peripheral vascular intervention. Current smokers were less likely to have cardiac comorbidities, diabetes mellitus, or chronic kidney disease, but more likely to have chronic lung disease. Current smokers were also more likely to be depressed and have poorer general health status than former and non-smokers, however they had comparable PAD-specific health status at baseline.

Provision of Smoking Cessation Support

Overall, 359 (75.7%) smokers received some form of cessation intervention: the majority 350 (73.8%) received only physician advice to quit, 74 (15.6%) received referral to a formal smoking cessation counseling program, and only 50 (10.5%) received pharmacologic treatment or nicotine replacement therapy. For patients who were not referred to smoking cessation counseling, patient, medical and system reasons were reported as contributory factors in 7 (1.5%), 17 (3.6%) and 3 (0.6%) respectively; however no reason was documented in most patients (373, 78.7%). For patients who did not receive pharmacologic treatment, patient, medical and system reasons were reported as contributory factors in 9 (1.9%), 17 (3.6%) and 4 (0.8%) respectively; however no reason was documented in most patients (394, 83.1%).

Site variability in Provision of Smoking Cessation Support

There was significant site variability in provision of smoking cessation performance measures (Table S2 and Figure 1). Site variability for any cessation intervention (advice, counseling or nicotine replacement therapy), as assessed by median odds ratio (MOR) was 2.13 (95% confidence interval [CI]: 1.51, 3.69;<0.001). That is, between two randomly selected sites, there was, on average, a greater than 2-fold odds of receiving any cessation support at one random site, as compared with another. This variability was not influenced by

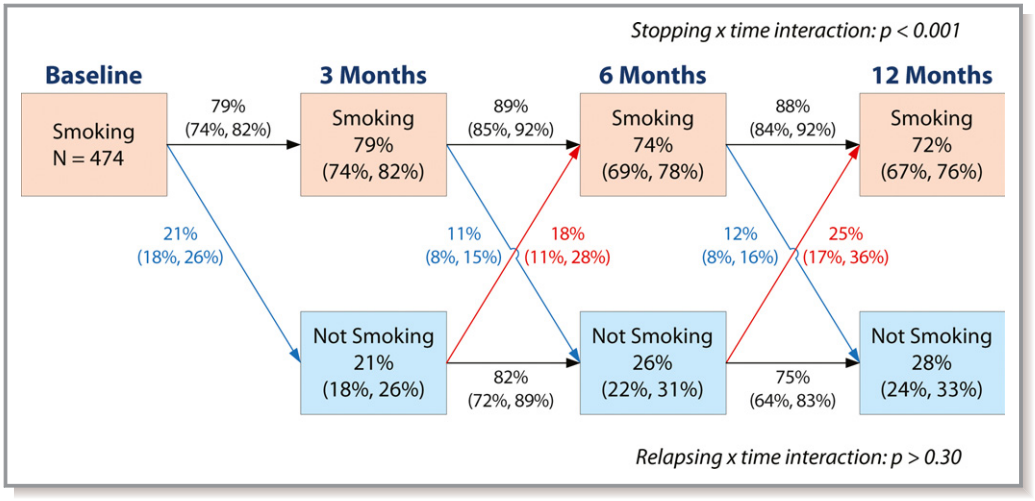

Figure 2. Transition probabilities between smoking and non-smoking states between follow-up time points among active smokers with symptomatic peripheral artery disease at initial visit. The blue arrows denote the probability of transition from smoking to non-smoking state (quitting) and red arrows denote the probability of transition from non-smoking to smoking state (relapse).

differences between countries (country-adjusted MOR=2.06; 95% CI: 1.45, 3.75; *P*<0.001). Greater variability was observed for referral to formal smoking cessation counseling programs or pharmacologic therapy and nicotine replacement therapy prescription (MOR=3.41 (95% CI: 2.15, 7.72), *P*<0.001), although a portion of this variation was attributable to differences between countries (country-adjusted MOR=2.27).

Predominant Smoking Patterns in Active Smokers Over the Course of a Year

Two thirds of active smokers continued to smoke throughout the 12 months of follow-up (Table S3). Approximately 1 in 10 patients relapsed after quitting at some point during follow-up. Among the patients who were sustained quitters (117/474, 24.6%), most (63, 13.4%) quit within the first 3 months of follow-up.

Transition Probabilities Between Smoking and Non-Smoking States on Follow-Up Among Active Smokers at Initial Visit

Among active smokers at baseline, the probability of smoking at 12 months was 72% (95% CI: 67%–76%; Figure 2). The likelihood of stopping smoking was greatest at 3 months (21%, 95% CI: 18%–26%); among those who persisted smoking at 3 months, the rate of subsequently stopping was 11% (95% CI: 8%–15%) at 6 months and 12% (95% CI: 8%–16%) at 12 months; *P*<0.001 versus 3 months). Moreover, among patients who stopped smoking at some point, there was a notable likelihood of relapse by the next assessment (18% (95% CI: 11%–26%) from 3 to 6 months; 25% (95% CI: 17%–36%) from 6 to 12 months). In multivariable analysis, continued smoking at 3 months was the greatest predictor of future smoking behavior after adjustment for multiple patient factors (odds ratio for quitting: 0.28 [0.09, 0.93]; odds ratio for relapse: 3.50 [1.02, 11.95]) (Figure S2).

Country-Specific Smoking and Smoking Cessation Patterns

Country-specific variations in proportions of smokers at initial visit, provider adherence to smoking cessation measures and predominant smoking patterns over follow-up are described in Tables S3, S4 and Figures S3 and S4. The Netherlands had a higher proportion of current smokers as compared with Australia and the United States. Provision of smoking cessation support, including referral rates to formal cessation counseling, were low across all countries, but greater in the United States as compared with the Netherlands and Australia. While the United States had a steady sustained quit rate at all follow-up time points, the majority of sustained quitters in the Netherlands stopped smoking in the first 3 months, while those in Australia were more likely to quit after 3 to 6 months of follow-up.

Discussion

A critical intervention for patients with symptomatic PAD is to stop smoking. Among 1275 patients presenting with PAD symptoms to a specialty clinic across the United States, the Netherlands, and Australia, we found that over a third were active smokers at their initial visit. Chances of quitting were highest within the first 3 months of their initial vascular

provider visit (21% quit rate). The predominant strategy used by providers to help their smoking patients to quit was simply to tell them to stop, with less than 1 in 5 smokers being referred to a smoking cessation counseling program and only 1 in 10 receiving pharmacologic treatment or nicotine replacement therapy. Regardless of the intervention, there was substantial variability in smoking cessation interventions across sites. More importantly, we found that smoking patterns were dynamic over time, with a high rate of relapse, highlighting the need for repeated and continuous cessation support in patients with symptomatic PAD.

PORTRAIT is a large multicenter, international prospective registry of symptomatic patients with PAD and our findings significantly extend the extant literature on smoking patterns in patients with PAD. Previous reports that studied the prevalence of smoking and the use of cessation support in PAD patients have been largely cross-sectional, done in preprocedural, hospitalization settings or primary care settings, or relied exclusively on administrative codes.[16,17,28,29] The global REACH (Reduction of Atherothrombosis for Continued Health) registry found that 22% of patients with PAD were current smokers, a prevalence almost double that of patients with other forms of atherosclerotic disease.[18] More recently, an analysis of US National Ambulatory Medical Care Survey of primary and specialty clinic visits with various stages of PAD by Berger et al showed a 20% prevalence of current smokers.[17] Our study extends these prior findings by prospectively documenting smoking behavior in more than a third of patients with confirmed PAD being evaluated for new or worsening claudication symptoms in a specialty care setting. Moreover, we were able to follow these patients over a year to describe their treatments and smoking behaviors, which is, to our knowledge, the first insight into these patterns over time. In contrast to PAD, for other atherosclerotic disease states like coronary artery disease, numerous studies have shown a much higher rate of smoking cessation, counseling, and sustained quit rates in active smokers in various settings such as stable outpatients with coronary artery disease, myocardial infarction or elective percutaneous coronary intervention (PCI),[30–32] which might be related to mandatory performance measure reporting, increased awareness about the association of smoking and adverse outcomes among patients and providers, and increased motivation to quit after a life-threatening event such as myocardial infarction.

This study demonstrates the dynamic nature of smoking and smoking cessation among patients with PAD. More than a third of patients were current smokers when they presented to a PAD provider and half were former smokers. Two thirds of active smokers continued smoking throughout the year following their PAD clinic visit. The highest quit rate measured was at the time window immediately after the PAD evaluation (21%). Among those who initially quit, more than a third relapsed, underscoring the challenge of getting patients to stop smoking. Our data also show that this addiction disproportionately affects patients who are younger and more socioeconomically disadvantaged. The scope of this problem calls for concerted efforts aimed at continuous risk assessment for relapse and repeated efforts to provide evidence-based interventions to maximize smoking cessation outcomes in PAD.

Evidence-based treatments for tobacco cessation are widely available. Pharmacologic therapy or formal cessation counseling have been shown to be more effective and cost-efficient than physician advice alone in helping smokers quit.[8,14,33] Prior cross-sectional studies have shown smoking cessation measure prescription rates varying from 36% to 53% in patients with PAD in the primary care and specialty setting.[16,17] However, some of these studies relied on administrative codes and could not assess the symptom status of patients with PAD.[17] Our study showed that these more effective cessation support measures were heavily underutilized: as little as 11% received pharmacotherapy, and 16% received referral to formal cessation counseling. Wide variability was observed across sites in providing smoking cessation support: for an active smoker, there was a >2.5 to 3-fold odds in whether or not they were getting referred for cessation counseling in going from one site to another, even after adjusting for country differences. In our study, the cessation therapies were not predictors of quit or relapse states, however this finding may be secondary to limited power because of fewer number of events. Multiple PAD guidelines have given a grade 1 recommendation for providing smoking cessation support for actively smoking patients with PAD.[13,34,35] It has also been proposed as a performance measure by PAD experts,[36] however it has not yet been endorsed by National Quality Forum for PAD.[37] Vascular and cardiac specialists have a unique opportunity to emphasize smoking cessation when the patients present to them for treatment of severe symptoms related to PAD. But these patients will also need continuous and repeated reinforcements on smoking cessation, as we observed a high rate of relapse. Mandatory implementation of smoking cessation support provision as a quality metric for vascular specialty clinics and increased advocacy and outreach of professional vascular provider societies emphasizing repeated provision of cessation support at each visit or hospitalization by vascular disease providers is essential to achieve higher smoking cessation rates in this high-risk population. Furthermore, establishment of health systems' infrastructure to facilitate easy referral and access to smoking cessation counselors and programs by vascular specialists and patients could help increase the use of these services by clinicians and patients.

Given the cardiovascular, economic, societal, and financial effects of smoking in patients with PAD,[5,8,9,38,39] our study

suggests that a shift in thinking is needed in the management of PAD. Addiction disorders are increasingly managed as a chronic disease using individualized and evidence-based strategies.[40,41] Tobacco addiction deserves to be treated in the same way and screening and resources should be made available accordingly. Collaborative, interdisciplinary strategies at the system-level are likely needed to ensure consistent, ongoing cessation support in an evidence-based fashion. These systems need to not only address cessation at intake, but also need to recognize that relapse is common and that some patients, who initially do not respond to treatment, may be able to successfully quit later. Quality benchmarks should be developed and implemented so that all patients get consistent, high-quality of cessation interventions across different health systems.

The results of our study should be viewed in the context of the following potential limitations. We used patient-reported smoking status and did not confirm active smoking or abstinence with biochemical testing. Thus, there is a potential for misclassification of smoking status. However, prior research has shown that self-report correlates well with biochemical testing.[42,43] Also, as our study is a non-interventional observational study, the risk of bias towards misreporting of smoking status, if any, should be small. Our findings only reflected cessation activities conducted at the PAD clinic. Some cessation activities may have also occurred in the primary care physician's office; however, we did abstract data from the medical records of the specialty providers and if they were deferring treatment to the primary care providers this should have been documented and captured by our data collection process. Given our focus on PAD specialty clinics, our findings might not be reflective of the general PAD population which includes asymptomatic patients and those never referred for specialty care. However, given that smoking cessation is highlighted in specialty management guidelines and proposed performance measures for PAD, and that we captured the patients on their first visit to a specialty provider for management of their PAD symptoms, it is likely that the use of smoking cessation interventions is even lower in general practice. While we tried to capture patient, system, and medical reasons smoking support was not provided, no reason was documented for most of the patients who did not receive cessation support. As such, we could not determine the exact reason if any, smoking support was not provided by the PAD provider. Finally, even though we adjusted for multiple demographic, socioeconomic, psychosocial and clinical factors, there might be residual confounders (eg, passive smoke exposure, quality of smoking cessation support) which could potentially affect the patients' probabilities of abstinence and relapses. Also, as we had small numbers of quitting and relapse events on follow-up, we had limited power to identify additional potential predictors of smoking behavior.

In conclusion, our study provides contemporary real-world data on smoking behavior and smoking cessation practices in patients with PAD. More than a third of patients who present to specialty care for evaluation of claudication symptoms are actively smoking, and 72% of these patients are smoking 12 months later. Importantly, few patients receive formal cessation interventions. The dynamic nature of these patients' smoking practices also underscores the need for ongoing assessment of smoking, even among those who report that they have quit, and consistent offering of evidence-based cessation support. Future research should focus on identifying optimal strategies for implementing consistent cessation support.

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Author Contributions

Drs Patel and Smolderen had full access to all the data in the study and are guarantors of the work. Study concept and design: Patel, Jones, Smolderen; Acquisition, analysis, or interpretation of data: All authors; Drafting of initial manuscript: Patel; Critical revision of the manuscript for important intellectual content: All authors; Statistical analysis: Jones; Administrative, technical, or material support: Smolderen; Study supervision: Smolderen.

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organizations and sponsors of the study had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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ONLINE DATA SUPPLEMENT (For publication)

Underutilization of Evidence-Based Smoking Cessation Support Strategies Despite High Smoking Addiction Burden in Peripheral Arterial Disease Specialty Care: Insights from the International PORTRAIT registry

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Table S1: Covariates included in the multiple imputation to account for missing data regarding smoking assessments on follow-up.

Country	Diabetes	PAQ scores
Age	Coronary Artery Disease	EQ-5D VAS
Sex	Heart failure	PHQ-8 scores
Race	Stroke/Transient Ischemic Attack	GAD-2 screen
Married	Lung disease	PSS stress score
Social support	Kidney disease	Smoking cessation measures
Education	PAD characteristics	Smoking status
Financial status	Alcohol abuse	
PAD= Peripheral Artery Disease, PAQ= Peripheral Artery Questionnaire, EQ-5D VAS= EuroQOL-5 dimension Visual Analog Scale, PHQ-8= Patient Health Questionnaire-8, GAD-2= Generalized Anxiety Disorder-2; PSS= Perceived Stress Scale		

Table S2: Site variability in provider adherence to smoking cessation performance measure. Variability measured by Median Odds Ratios (95% confidence intervals) and p-values.

	Any Intervention	**Physician advice to stop smoking**	**Referral to cessation counseling**	**Pharmacologic Therapy and Nicotine replacement therapy**	**Referral to Cessation Counseling or Pharmacologic Therapy**
Site variation					
Unadjusted	**2.13 (1.51, 3.69) p<0.001**	**2.21 (1.57, 3.90) p<0.001**	**4.48 (2.54, 12.31) p<0.001**	**2.01 (1.35, 3.68) p=0.002**	**3.41 (2.15, 7.72) p<0.001**
Adjusted for country	**2.06 (1.45, 3.75) p<0.001**	**2.20 (1.53, 4.11) p<0.001**	**3.26 (1.92, 8.57) p<0.001**	1.00 (1.00, 1.81) p=0.99	**2.27 (1.54, 4.56) p<0.001**

Table S3: Predominant smoking patterns on follow-up among active smokers with symptomatic peripheral arterial disease at initial visit. Presented as N (%) for patients with available smoking status assessments on follow-up. Persistent smokers= patient reported smoking at baseline and 3, 6 and 12 months of follow-up; Sustained quitters= Patient stopped smoking at that time point and remained quit through 12 months of follow-up (12 month- patient stopped smoking at 12 months- follow-up not available); Relapsers= Active smokers at baseline who reported stopping smoking at any time point on follow-up, but restarted smoking thereafter.

	Overall (N=474)	**Country**		
		United States (N=241)	**Netherlands (N=201)**	**Australia (N=32)**
Persistent smokers	311 (65.5%)	162 (67.4%)	129 (64.3%)	19 (59.7%)
Sustained quitters 3months 6 months 12 months	 63 (13.4%) 22 (4.7%) 32 (6.7%)	 22 (9.0%) 13 (5.2%) 18 (7.5%)	 39 (19.6%) 6 (2.8%) 10 (4.9%)	 2 (6.9%) 4 (13.4%) 4 (12.7%)
Relapsers	46 (9.6%)	26 (10.9%)	17 (8.5%)	2 (7.3%)

Table S4: Overall and country-specific provider adherence to smoking cessation performance measure.

	Overall n = 474	**USA n = 241**	**Netherlands n = 201**	**Australia n = 32**	**p-value**
Smoking cessation performance measure adherence	359 (75.7%)	196 (81.3%)	139 (69.2%)	24 (75.0%)	0.01
Physician advice	350 (73.8%)	190 (78.8%)	136 (67.7%)	24 (75.0%)	0.03
Referral to smoking cessation counseling	74 (15.6%)	67 (27.8%)	6 (3.0%)	1 (3.1%)	< 0.001
Pharmacologic treatment for smoking cessation (including nicotine replacement therapy)	50 (10.5%)	40 (16.6%)	5 (2.5%)	5 (15.6%)	< 0.001
Continuous variables compared using one-way analysis of variance. *Categorical variables compared using chi-square or Fisher's exact test.*					

Figure S1: Transition probabilities between smoking and non-smoking states between follow-up time points among active smokers with symptomatic peripheral arterial disease at initial visit. The blue arrows denote the probability of transition from smoking to non-smoking state (abstinence) and red arrows denote the probability of transition from non-smoking to smoking state (relapse) (Proportions derived from raw data with available smoking status assessments, Fig. 2 in the manuscript represents probabilities derived from imputed data after imputing 14% missing data for smoking status assessments on follow-up).

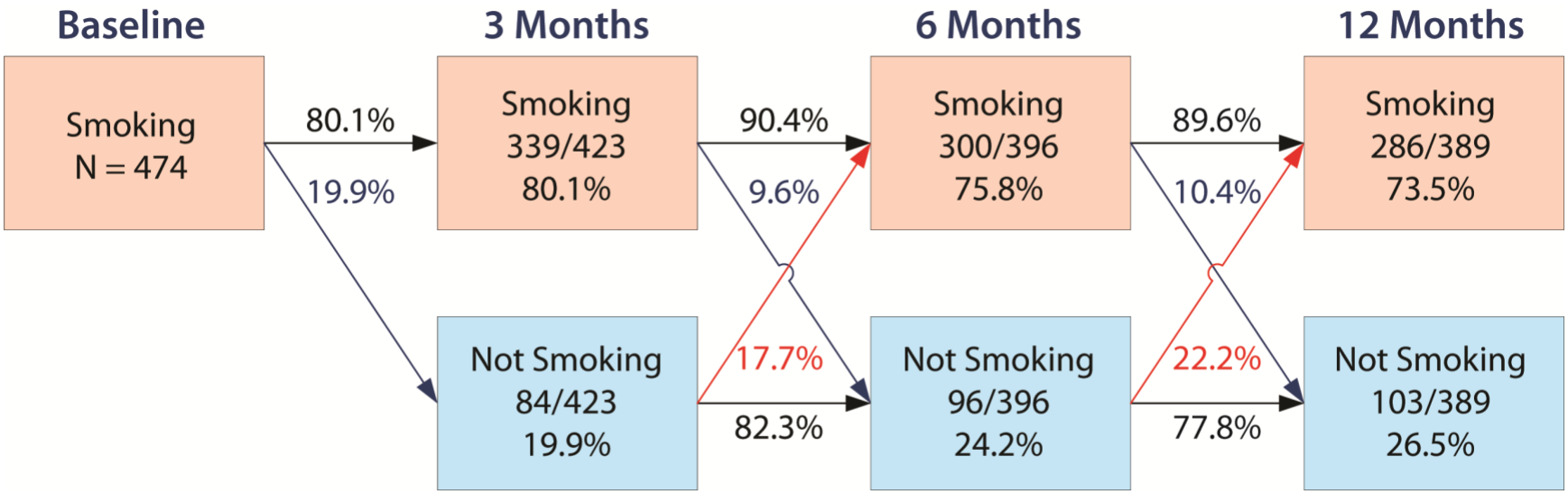

Figure S2: Multivariable predictors of quitting and relapse states at follow-up among active smokers at initial visit presenting with symptomatic peripheral arterial disease. Quitting was defined as transition from smoking to non-smoking state between consecutive time points and Relapse was defined as transition from non-smoking to smoking state between consecutive time points (after 3 months). Estimates are Odds Ratios (95% Confidence Intervals) calculated from transition models.

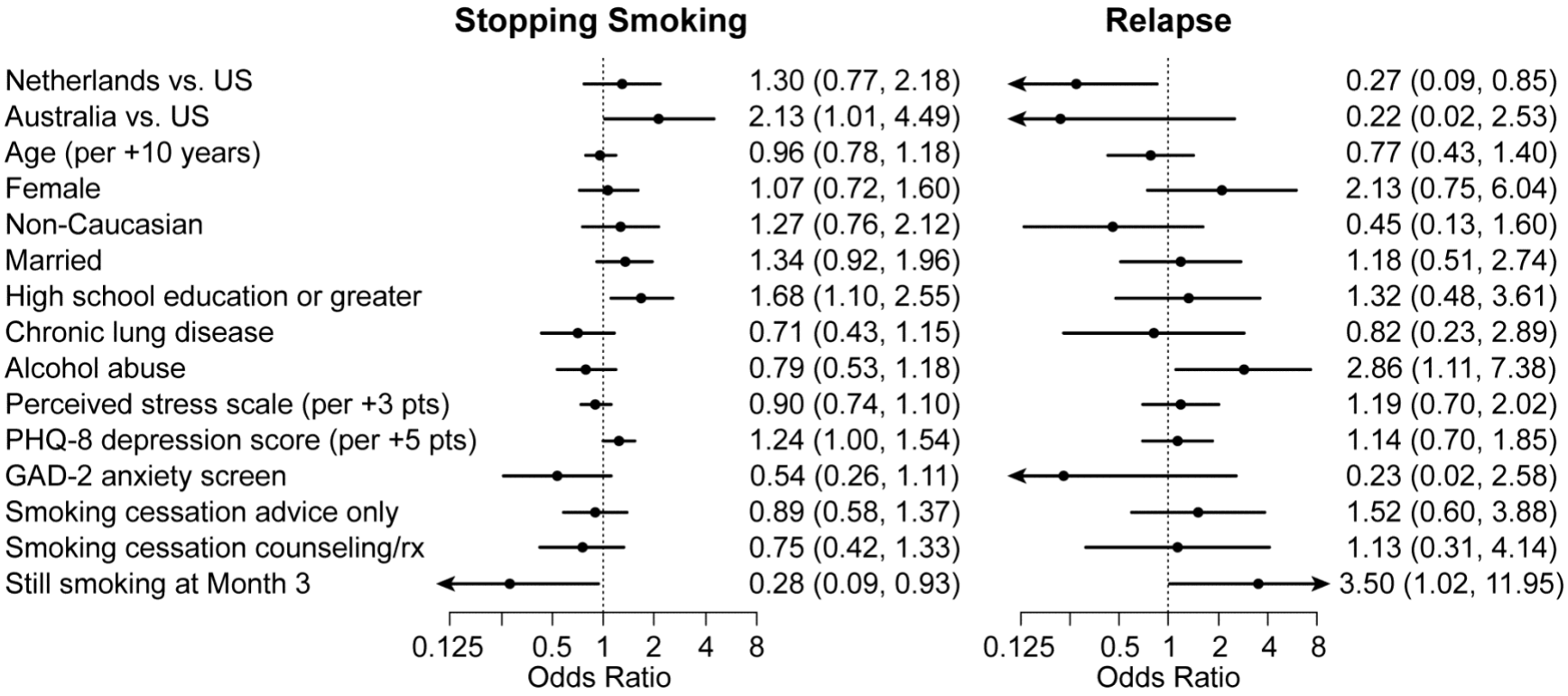

Figure S3: **Country-specific smoking patterns in patients with symptomatic peripheral arterial disease at initial presentation.**

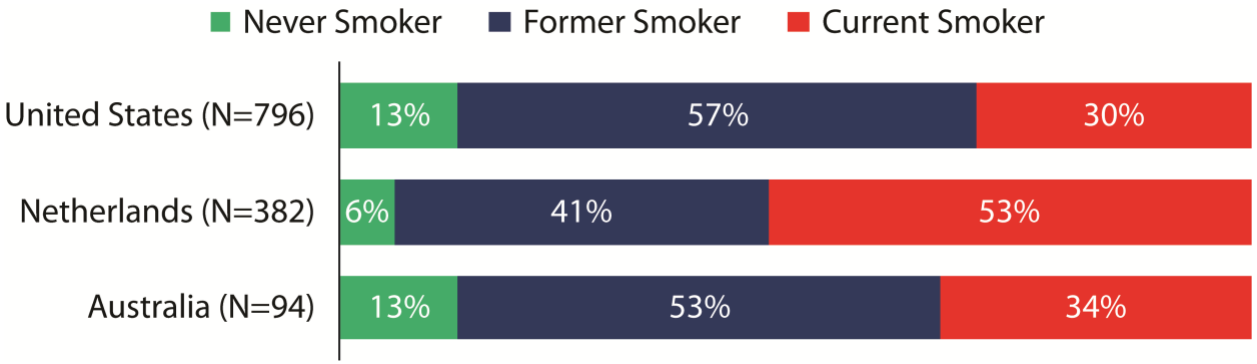

Figure S4: Country-specific transition probabilities between smoking and non-smoking states between follow-up time points among active smokers with symptomatic peripheral arterial disease at initial visit (Imputed data). The blue arrows denote the probability of transition from smoking to non-smoking state (abstinence) and red arrows denote the probability of transition from non-smoking to smoking state (relapse).