Adherence to Guideline-Recommended Therapy—Including Supervised Exercise Therapy Referral—Across Peripheral Artery Disease Specialty Clinics: Insights From the International PORTRAIT Registry

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Background—Underuse of guideline-recommended therapy in peripheral artery disease (PAD) in administrative and procedural databases has been described, but reports on medically managed patients and referral to supervised exercise therapy (SET) in PAD are lacking. We aimed to document the use of PAD guideline-recommended therapy, including SET in patients with PAD symptoms consulting a specialty clinic across 3 countries.

Methods and Results—The 16-center PORTRAIT (Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories) registry enrolled 1275 patients with new or an exacerbation of PAD symptoms (2011–2015). We prospectively documented antiplatelet medications, statins, smoking cessation counseling and/or therapy, and referral to SET: "2 quality measures" referred to the use of both statin and antiplatelet medications; "4 quality measures" to receiving all 4 measures. Median odds ratios were calculated to quantify treatment variation across sites. A total of 89% patients were on antiplatelets, 83% on statins, and 23% had been referred to SET. Of 455 current smokers, 342 (72%) patients received smoking cessation therapy/counseling. Overall, 77.2% of patients received “2 quality measures” and 19.7% “4 quality measures.” The median odds ratio for 2 quality measures was 2.13 (95% CI, 1.61–3.56; P<0.001) and for 4 quality measures was 5.43 (95% CI, 2.84–17.91; P<0.001). Variability in adherence was not explained by country, except for referral to SET. The odds for SET referral in The Netherlands (70% referral rate) was nearly 100 times greater than in US sites (2% referral rate).

Conclusions—Not all patients who have undergone a PAD workup at a specialty care facility are treated with evidence-based care, especially so for SET. (J Am Heart Assoc. 2020;9:e012541. DOI: 10.1161/JAHA.119.012541.)

Key Words: medical management • peripheral artery disease • quality of care

Worldwide, more than 200 million individuals suffer from peripheral artery disease (PAD).1 Lower-extremity PAD is a burdensome condition caused by the underlying process of atherosclerosis that manifests itself in the leg arteries. It represents a spectrum of clinical manifestations that can include atypical lower-extremity symptoms, intermittent claudication, rest pain, and tissue loss secondary to ischemia.2 Patients with PAD are at a significantly increased risk for morbidity and mortality attributable to cardiovascular events not involving the lower extremities.3,4 As such, medical and lifestyle interventions constitute essential elements of evidence-based PAD care, both from a perspective of improving cardiovascular mortality as well as limb-related outcomes.

As part of the evidence-based risk management of PAD, 4 noninvasive treatments are recommended by the American College of Cardiology/American Heart Association performance measures for PAD: (1) statin medications, (2) antiplatelet therapy, (3) smoking cessation therapy and/or counseling, and (4) referral to a PAD-specific supervised exercise training (SET) program.2,5,6 These quality metrics for PAD care have since then been retained in several guideline statements, including the recent 2016 PAD treatment guidelines.2 Several studies have demonstrated low adherence rates to these
Clinical Perspective

What Is New?

- When patients receive a workup for peripheral artery disease (PAD) symptoms in the specialty care setting, only 1 in 5 receive all eligible evidence-based medical management quality measures for PAD, with high variability across institutions.
- Especially a lack of referral to supervised exercise therapy stands out in the US context versus European specialty care settings.

What Are the Clinical Implications?

- Structural barriers for realizing optimal quality PAD care in the specialty setting need to be explored and addressed as without realizing optimal quality care, patients suffering from PAD remain disadvantaged in their ability to manage their PAD and cardiovascular risk.

Performance measures for patients with PAD as compared with patients with other forms of cardiovascular disease.\textsuperscript{7–11} This evidence came from retrospective analyses using administrative data\textsuperscript{11} or from procedure-based databases only.\textsuperscript{12} There is a lack of prospective studies describing adherence rates to PAD treatment guidelines, and, in particular, evidence on referral patterns for SET is missing. Little is known about the variability in adherence to evidence-based PAD care across treatment sites and healthcare settings.

To address this gap in knowledge, we aimed to quantify rate of adherence to PAD performance measures as it relates to medical therapy and SET in subspecialty vascular centers for patients presenting with new-onset or an exacerbation of PAD symptoms. Next, we examined how adherence to these measures varies across sites.

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 (Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories) group on the website.\textsuperscript{13}

Study Population

The PORTRAIT study is a multicenter, prospective study of patients presenting for specialty vascular care with new-onset, or an exacerbation of, lower-extremity symptoms. The methods have been described previously.\textsuperscript{14} Briefly, patients with new onset or worsening of PAD symptoms were screened for enrollment at the time of referral to subspecialty vascular care sites. Patients with a resting ankle brachial index \( \leq 0.90 \) or drop in postexercise ankle pressure of \( \geq 20 \) mm Hg were eligible for inclusion. Patients with a noncompressible ankle brachial index \( \geq 1.30 \), patients presenting with ischemic rest pain, ulceration, or gangrene (Rutherford grade II–III), or those who had undergone a lower-limb surgical or endovascular procedure in the past year in the ipsilateral leg were excluded. Other exclusion criteria were non-English, Spanish, or Dutch speaking, hard of hearing, unable to provide informed consent, or currently a prisoner. The participating centers consisted of 10 sites in the United States, 5 sites in The Netherlands, and 1 site in Australia (16 total). Institutional review board approval was obtained for the study at each participating site. Diagnostic enrollment criteria for PAD consisted of an ankle brachial index with PAD defined as an ankle brachial index \( \leq 0.90 \) or a postexercise drop in ankle blood pressure \( \geq 20 \) mm Hg. Before the initiation of subspecialty treatment, baseline demographic, socioeconomic, and clinical data were obtained by trained data collectors.

Primary Outcomes

The primary outcome of the study was the adherence rate to 4 noninvasive interventions first recommended by the 2010 American College of Cardiology/American Heart Association PAD performance measures, which mirror the recommendations of the current 2016 treatment guidelines:\textsuperscript{15} (1) antiplatelet therapy, (2) statin therapy, (3) SET, and (4) smoking cessation counseling.\textsuperscript{5,15,16} Adherence rates were collected after the PAD workup that patients received at the subspecialty clinic as part of their routine care to reflect contemporary subspecialty treatment practices.

Antiplatelet therapy was defined as the use of aspirin at a dose of 75 to 325 mg daily or clopidogrel at a dose of 75 mg daily. Statin therapy was defined as the prescription of any available 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. For both medications, patients were excluded from the denominator if there were documented medical reasons or patient reasons as to why patients would not be eligible to receive this metric.\textsuperscript{2,5} The smoking cessation performance measure included verbal instructions, referral to a special program or formal counseling, as well as pharmacological therapy.\textsuperscript{5} For the purposes of our study, we considered achieving either of these criteria as a successful effort to meet the recommendation. Nonsmokers were excluded from the analysis of the smoking cessation measure. SET was defined as referral to a formal supervised exercise program. Unstructured and home-based exercise therapy was not considered to have met the recommendation, given that this was not supported by the 2010 American College of Cardiology/American Heart
Association performance measures and is currently not a Class I recommendation.2,5 Per the American College of Cardiology/American Heart Association performance measures, patients were excluded from the denominator if there were documented medical reasons for not offering SET (eg, heart failure).2,5 If a patient had a contraindication or if the measure did not apply to them (such as smoking), they were marked as having achieved that quality measure.

We further analyzed adherence to combinations of the measures: (1) adherence to the 2 pharmacological measures (being on a statin and antiplatelet therapy or “2 quality measures”) and (2) adherence to all measures (4 quality measures) for smokers and participation in 3 performance measures [antiplatelets, statins, and SET] for nonsmokers or “4 quality measures”). Variability in achieving rates of “2 quality measures” and “4 quality measures” across sites were calculated using median odds ratios (MORs). The MOR represents the median value of the odds for receiving the performance measures for 2 statistically identical patients being treated at 1 random clinic versus another. For example, an MOR of 1.5 suggests that, on average, a patient treated at 1 clinic has a 50% higher odds of receiving the treatment than if they had presented at another clinic.17

### Statistical Analysis

Descriptive statistics for continuous variables are expressed as means with SD and for categorical variables as frequencies and percentages. Comparisons were performed by the receipt of 2 quality measures as well as by 4 quality measures using Student t tests or Mann–Whitney U tests for continuous variables and chi-square tests or Fisher’s exact tests for categorical variables.

Achievement of each of the individual performance measures was calculated by study site, and then adherence rates were compared using multivariable, hierarchical, logistic regression models with site as a random effect. The odds of achieving the study variable of interest is expressed as odds ratios plus 95% CIs. To compare practice patterns across study sites, MORs were calculated for each of the study variables to quantify variations in treatment rates of achieving “2 quality measures” and “4 quality measures.”

All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC). A 2-sided P value of <0.05 was considered to be statistically significant for all analyses.

### Results

A total of 1275 patients with new or an exacerbation of symptoms prompting referral to a vascular specialty clinic were enrolled in the study. Patient baseline demographics are represented in Table. After the first PORTRAIT subspecialty site visit, 1104 (89.0%) patients with new or worsening symptoms of PAD were prescribed antiplatelet medications, 1055 (82.7%) were prescribed a statin, and 280 (23.3%) were referred to a supervised exercise program. There were 455 (35.7%) current smokers; of those patients, 342 (75.2%) had been referred to or counseled about smoking cessation (Table). Patients receiving 2 quality measures (antiplatelet therapy and statin) were more likely to be male and more likely to have ischemic cardiovascular risk factors as compared with those who did not receive 2 quality measures. Patients receiving 4 quality measures (antiplatelet therapy, statin, smoking cessation, and supervised exercise therapy referral) were more likely to be from The Netherlands, white, married, lower education, had some money left over at the end of the month, and had less cardiovascular risk factors (Table).

Across sites, there was a high degree of variability in the use of performance measures for high-quality care (Figure 1A through 1D). For example, the rate of prescribing antiplatelet therapy across sites ranged from 63% to 100% (Figure 1A), with a median odds ratio of 2.93 (95% CI, 1.94–6.17; P<0.0001). The MOR for achieving the other 3 individual performance measures were also high: 2.11 (95% CI, 1.57–3.63; P<0.0001) for statin therapy; 3.06 (95% CI, 1.90–7.06; P<0.001) for smoking cessation therapy; and 4.98 (95% CI, 2.73–15.46; P<0.0001) for SET.

There was little difference between international sites and US sites in prescribing antiplatelets or statins or for achieving the smoking cessation measure. In contrast, the odds that patients in The Netherlands were referred to SET was nearly 100 times (odds ratio=97.42; 95% CI, 9.79–969.59; P<0.001) greater than its use in the US sites; and patients in Australia had a 27 times greater odds of referral to SET (odds ratio=27.38; 95% CI, 0.42–1771.47; P=0.11) than US sites (Figure 1D).

There was also a high degree of variability in achieving “2 quality measures” and “4 quality measures” (Figure 2). For the entire cohort, there were 984 (77.2%) patients who achieved “2 quality measures” and 251 (19.7%) who achieved “4 quality measures.” The MOR for achieving 2 quality measures was 2.13 (95% CI, 1.61–3.56; P<0.001) and for 4 quality measures was 5.43 (95% CI, 2.84–17.91; P<0.001). There was no difference in achieving 2 quality measures between patients in the United States (77.9%), The Netherlands (77.8%), and Australia (68.4%; P=0.107). However, there was a marked difference in the rate of achieving 4 quality measures in the United States (4.6%) versus The Netherlands (51.7%) and Australia (16.8%; P<0.001).

### Discussion

In the PORTRAIT registry, we found that although adherence rates to 2 pharmacological interventions—antiplatelet

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Table. Baseline Patient Characteristics for the Overall Sample and by Receipt of 2 Quality Measures and by 4 Quality Measures

|                          | Overall Sample (n=1275) | 2 Quality Measures | 4 Quality Measures |  P Value |  P Value |
|--------------------------|-------------------------|--------------------|--------------------|----------|----------|
|                          | Yes (n=984; 77%)        | No (n=291; 23%)    | Yes (n=251; 20%)   |          |          |
| Age, y                   | 67.6±9.4                | 67.7±10.1          | 67.9±9.7           | 0.88     | 0.019    |
| Female sex               | 483 (37.9%)             | 128 (44.0%)        | 398 (38.9%)        | 0.013    | 0.11     |
| Country                  |                         |                    |                    | 0.11     | <0.001   |
| (1) United States        | 798 (62.5%)             | 176 (60.5%)        | 37 (14.7%)         | 0.013    |          |
| (2) Netherlands          | 384 (30.1%)             | 85 (29.2%)         | 198 (78.9%)        | 0.88     |          |
| (3) Australia            | 95 (7.4%)               | 30 (10.3%)         | 79 (7.7%)          | 0.013    |          |
| White                    | 1047 (82.1%)            | 237 (81.4%)        | 810 (79.1%)        | 0.73     | <0.001   |
| Hispanic                 | 17 (1.9%)               | 1 (0.5%)           | 15 (1.8%)          | 0.14     | 0.27     |
| Married                  | 753 (59.4%)             | 171 (59.2%)        | 585 (57.5%)        | 0.93     | 0.004    |
| High school education or above | 872 (69.0%)          | 200 (69.4%)        | 755 (74.1%)        | 0.87     | <0.001   |
| Active working status    | 303 (23.8%)             | 72 (24.7%)         | 236 (23.0%)        | 0.67     | 0.23     |
| Finances at end of month |                         |                    |                    | 0.79     | 0.05     |
| Some money left over     | 684 (55.1%)             | 150 (54.0%)        | 534 (53.5%)        | 0.14     |          |
| Just enough to makes ends meet | 423 (34.1%)        | 95 (34.2%)         | 352 (35.2%)        | 0.27     |          |
| Not enough to makes ends meet | 134 (10.8%)           | 33 (11.9%)         | 113 (11.3%)        | 0.93     |          |
| Atrial fibrillation      | 143 (11.2%)             | 47 (16.2%)         | 124 (12.1%)        | 0.002    |          |
| Current smokers          | 455 (35.7%)             | 106 (44.4%)        | 360 (40.6%)        | 0.27     |          |
| Congestive heart failure | 128 (10.0%)             | 24 (8.2%)          | 119 (11.6%)        | 0.27     | <0.001   |
| Dyslipidemia             | 1016 (79.6%)            | 179 (61.5%)        | 833 (81.3%)        | <0.001   |          |
| Hypertension             | 1018 (79.7%)            | 222 (76.3%)        | 846 (82.6%)        | 0.09     | <0.001   |
| History of TIA/CVA       | 146 (11.4%)             | 24 (8.2%)          | 114 (11.1%)        | 0.05     | 0.47     |
| History of angina pectoris | 178 (13.9%)            | 30 (10.3%)         | 142 (13.9%)        | 0.040    | 0.85     |
| Previous myocardial infarction | 244 (19.1%)         | 38 (13.1%)         | 202 (19.7%)        | 0.003    | 0.17     |
| History of PCI/CABG      | 447 (35.0%)             | 65 (22.3%)         | 382 (37.3%)        | <0.001   | <0.001   |
| Chronic kidney disease   | 142 (11.1%)             | 29 (10.0%)         | 126 (12.3%)        | 0.47     | 0.007    |
| Chronic lung disease     | 218 (17.1%)             | 56 (19.2%)         | 171 (16.7%)        | 0.27     | 0.44     |
| History of cancer        | 128 (10.0%)             | 32 (11.0%)         | 104 (10.2%)        | 0.54     | 0.78     |
| History of depression    | 102 (8.0%)              | 13 (4.5%)          | 41 (4.0%)          | 0.76     | 0.58     |
| Diabetes mellitus        | 424 (33.2%)             | 81 (27.8%)         | 367 (35.8%)        | 0.025    | <0.001   |
| ABI                      | 0.67±0.19               | 0.68±0.18          | 0.67±0.19          | 0.14     | 0.06     |
| Adherence to antiplatelet therapy | 1104 (89.0%)     | 143 (51.3%)        | 864 (86.4%)        | <0.001   | <0.001   |
| Adherence to statin therapy | 1055 (82.7%)         | 71 (24.4%)         | 804 (78.5%)        | <0.001   | <0.001   |
| Performance measure for supervised exercise therapy | 280 (23.3%)       | 52 (18.8%)         | 84 (8.3%)          | 0.044    | <0.001   |
| Performance measure for smoking cessation | 342 (75.2%)       | 80 (75.5%)         | 247 (68.6%)        | 0.93     | <0.001   |
| Primary PAD treatment    |                         |                    |                    |          |          |
| Medical therapy only     | 932 (74.8%)             | 207 (73.4%)        | 739 (73.6%)        | 0.45     | 0.13     |
| Endovascular intervention | 275 (22.1%)             | 63 (22.3%)         | 233 (22.3%)        | 0.84     |          |
| Surgical intervention    | 39 (3.1%)               | 12 (4.3%)          | 32 (3.2%)          | 0.84     |          |
| Unsupervised exercise referral | 145 (17.0%)          | 33 (16.5%)         | 127 (15.8%)        | <0.001   |          |

Continued
therapy and statin therapy—were high overall, low adherence rates were observed for the nonpharmacological interventions—smoking cessation and SET. Although 2 quality measures (antiplatelet and statin therapy) rates were higher in the United States, 4 quality measures (antiplatelet, statin therapy, smoking cessation, and SET) rates were higher in non-US countries. A high degree of variability in quality of care between vascular specialty centers was observed, especially so for the nonpharmacological interventions offered to patients with PAD. The most extreme example of this variability was adherence to SET: As high as 90% adherence rates were observed at some sites, whereas other centers referred no patients to SET. Centers with the highest performance rates of adherence to SET were predominantly sites from The Netherlands. SET was rarely prescribed in the US sites.

Both statins and antiplatelet therapy have robust data to support their use in PAD. Statins and antithrombotic therapy improve morbidity and mortality in patients with PAD and cardiovascular disease and improve limb-related outcomes in PAD.12,18–20 Despite these compelling data, patients with PAD have historically been prescribed statins and antiplatelet therapy less often than patients with CAD or cerebrovascular disease.7,9–11,21,22 Although underuse of guideline-recommended therapy in PAD has been documented in several administrative databases,12,16,23,24 PORTRAIT is the first study to have prospectively documented these measures in the specialty setting.

It is striking that up to 90% of patients with PAD in The Netherlands were prescribed SET and little use in the United States. The referral network to SET facilities in The Netherlands is well developed and the therapy is reimbursed by patients’ health insurance.25 In contrast, US providers have only since 2017 been given the option of prescribing SET as a Centers for Medicare and Medicaid Services reimbursable therapy.26 Given that reimbursement is an important criterion to successfully implement SET, an availability of specialized SET centers and trained staff as well as education and experience of providers on the benefits of SET are key ingredients of SET implementation success.27 Other barriers, such as availability and unawareness, may remain.25,27,28 Given that prevalence of PAD and healthcare costs to care for this population are both rising,1 barriers to SET access should be further studied, given that SET may be a potent instrument to cost-effectively manage lower-extremity symptoms in PAD.29

Another powerful, but underused, risk-mitigation strategy in PAD is smoking cessation support for patients that are active smokers. Continued smoking in PAD comes with a high cost, both from the patient’s and societal perspective.12,30–33 Only 75% of current smokers were counseled against tobacco use or referred for smoking cessation counseling. An issue in achieving these performance measures may be the role of insurance or other third-party payers. For tobacco cessation therapies, patients are more likely to participate in tobacco cessation programs and adhere to physician recommendations if insurance companies cover nicotine gum, etc, and overall cessation rates improved when compared with patients for whom those therapies were not covered.21 Besides coverage issues, awareness about evidence-based therapies for smoking cessation,30,34,35 chronic monitoring, and management strategies as well as health-system–supported structural programs that facilitate easy referral to evidence-based programs are critical to improve performance on this measure.

Adherence to pharmacotherapy measures was relatively high in this study. An 89% and 83% adherence rate was observed for antiplatelet and statin medications, respectively. These rates are higher than those documented from earlier databases, which did not specifically focus on the vascular specialty setting, but rather the outpatient setting in general.11 As such, our PAD performance adherence estimates

Table. Continued

| Site location                  | Overall Sample (n=1275) | 2 Quality Measures | 4 Quality Measures | P Value |
|-------------------------------|------------------------|--------------------|--------------------|---------|
| Suburban location             | 130 (10.2%)            | 101 (10.3%)        | 29 (10.0%)         | 0.017   |
| Urban location                | 1103 (86.5%)           | 843 (85.7%)        | 260 (89.3%)        | 0.001   |
| Urban/rural location          | 42 (3.3%)              | 40 (4.1%)          | 2 (0.7%)           | 0.86    |
| Site characteristics          |                        |                    |                    | <0.001  |
| Nonacademic                   | 492 (38.6%)            | 381 (38.7%)        | 492 (38.6%)        | 0.251   |
| University affiliated         | 783 (61.4%)            | 603 (61.3%)        | 783 (61.4%)        | 0.587   |

ABI indicates ankle-brachial index; CAGB, coronary artery bypass grafting; CVA, cerebrovascular attack; PAD, peripheral artery disease; PCI, percutaneous intervention; TIA, transient ischemic attack.

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for the vascular specialty setting add to our current understanding of how PAD is managed.

There are limitations that must be acknowledged in the PORTRAIT study. PORTRAIT data represent a selection of 16 vascular specialty centers, and it is unclear how their performance rates extend to other specialty centers that were not in our study. Next, enrollment sites came from 3 different countries, and policy differences as well as differences in the landscape of healthcare organization are factors that need to be taken into account when interpreting our findings. Another limitation is that we relied on abstracted information from medical records, and the potential for misclassification attributable to nondocumentation is a possibility. Finally, PORTRAIT data in the United States were collected at a time when SET was defined as a guideline-recommended therapy but without reimbursement framework from the Centers for Medicare and Medicaid Services. This changed in 2017, and it is uncertain how this development has affected current SET prescription rates in the United States.

Conclusions

PAD performance measures that include pharmacotherapy (statins and antiplatelet therapy) seem to be relatively feasible
and well adhered to by vascular specialists. Although key strategies to lower PAD risk and improve patients’ outcomes, adherence to nonpharmacological risk-mitigation strategies, including smoking cessation referral and SET, is not well realized in the specialty care setting. Along with the great variability in performance rates across sites, this requires future deeper exploration as to why nonpharmacological guideline-recommended risk-prevention strategies are not successfully realized. Structural reasons, including coverage, availability, as well as patient, practice, and provider preferences, are factors that will need to be considered in our search to optimize key risk-management strategies and outcomes for PAD.

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