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Patient-Reported Outcome Measures in Symptomatic, Non–Limb-Threatening Peripheral Artery Disease: A State-of-the-Art Review

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ABSTRACT: Patient-reported outcome measures (PROMs) are health outcomes directly reported by the patient that can be used to measure the effect of disease and treatments on patient perceived well-being. This review summarizes current evidence regarding the validation of PROMs in people with symptomatic, nonlimb-threatening peripheral artery disease. A literature search was conducted to identify studies of symptomatic peripheral artery disease without limb-threatening ischemia that included PROMs and had sample sizes ≥25. PROMs were summarized along a continuum of validation using classical test theory framework and according to whether they fulfilled defined criteria for (1) content validity; (2) psychometric validation; and (3) further validation evidence base expansion. Of 2198 articles identified, 157 (7.1%) met inclusion criteria. Twenty-four PROMs in patients with symptomatic peripheral artery disease were reviewed. Among disease-specific PROMs, 8 of 15 had excellent reliability as measured by a Cronbach alpha ≥0.80. Based on established criteria for PROM responsiveness, 6 of 15 disease-specific PROMs demonstrated excellent sensitivity to change. Of these, the disease-specific peripheral artery questionnaire, vascular quality of life questionnaire, and walking impairment questionnaire met criteria for validation at each stage of the continuum. For generic (nondisease specific) PROMs, the European Quality of Life 5-Dimension and SF-36 had the most extensive evidence of validation. Evidence from this review can inform selection of PROMs aligned with scientific and clinical goals, given the variable degree of validation and potential complementary nature of the measures.

Key Words: artery ■ ischemia ■ psychometric ■ quality of life ■ sample size

Peripheral artery disease (PAD) affects 200 million people worldwide, including at least 8 million people in the United States. Individuals with PAD have greater functional impairment and mobility loss than those without PAD.[1,2] In addition to cardiovascular risk management, PAD management focuses on improving function, walking performance, and quality of life with treatment options consisting of exercise therapy, revascularization, and 2 medications (cilostazol and pentoxifylline) approved by the US Food and Drug Administration.[3]

Most randomized trials of interventions that improve walking performance in PAD use objective testing, such as treadmill walking distance and the 6-minute walk test, to measure the efficacy of these interventions.[4,5] Increasingly, and in combination with Food and Drug Administration guidance on patient-reported outcome measures (PROMs),[6] there is growing recognition of the importance of end points measuring patients' health status and quality of life. It is unclear, however, to what degree PROMs and health status measures used in PAD have attained criteria for validation necessary for use in future research and clinical practice. Recognizing this gap in knowledge, a multi-stakeholder task force was convened to better understand priorities for advancing the scientific rigor and validation of PROMs in symptomatic lower-extremity PAD. The group concluded that given the distinct clinical characteristics and treatment goals of patients with

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Nonstandard Abbreviations and Acronyms

CLTI	critical limb threatening ischemia
EQ-5D	European Quality of Life 5-Dimension
MCID	minimally clinically important difference
PAD	peripheral artery disease
PAQ	peripheral artery questionnaire
PROM	patient-reported outcome measures
VascuQoL	vascular quality of life questionnaire
WIQ	walking impairment questionnaire

chronic limb-threatening ischemia (CLTI) (including ischemic rest pain and tissue loss) compared with symptomatic PAD without CLTI, distinct evaluations of PROMS were necessary for these different populations within the spectrum of PAD.

We conducted a state-of-the-art review of PROMs employed in patients with symptomatic PAD without CLTI to evaluate the degree to which they have been validated in this population. Following the classical test theory framework,[7,8] the following criteria were evaluated: (1) content validity (including patient and clinician input to derive conceptual framework and items); (2) psychometric validation (construct and clinical validity, reliability, test-retest reliability, sensitivity to change); and (3) validation evidence base expansion (language translations and cultural adaptations, use in comparative effectiveness research, established minimally clinically important differences [MCID], predictive validity). This review focused on symptomatic PAD, defined as mild to severe PAD (Rutherford stages 1–3) associated with ischemic leg symptoms, including claudication and atypical ischemic leg symptoms, but excluded those with ischemic rest pain or tissue loss (Rutherford 4–6).[9]

PATIENT-REPORTED OUTCOME MEASURES

According to the Food and Drug Administration–NIH BEST (Biomarkers, End Points and Other Tools) working group, "a patient-reported outcomes measure is a measurement based on a report that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else."[10] PROMs can be used for outcome assessments of therapeutic evaluations, monitoring disease processes, and comparing disease states as evaluated by those with the disease (ie, PAD). Additional information about PROMS can be found in the Appendix in the Supplemental Material, including a depiction of how these constructs relate to PAD.

STAKEHOLDER CONVENTION

In 2018, Vascular Cures (a nonprofit 501(c)(3) organization, Redwood City, CA) convened the PROM-PAD Working Group to address shortcomings in outcome measures in symptomatic PAD. A multidisciplinary group of clinicians, scientists, regulatory experts, payers, industry leaders, and patients met over 2 years to develop consensus on the current state of outcomes measures in symptomatic PAD and to identify priority projects to meaningfully advance the field for the benefit of all stakeholders (Table S1; https://vascularcures.org/pad-working-group/). In brief, these meetings focused on examining the current validation work for PROMs in symptomatic PAD and identifying opportunities to advance this validation work to improve the performance of these instruments for the purposes of clinical care and research.

REVIEW OF THE LITERATURE

To further understand the extent to which health status measures applied to patients with symptomatic PAD have attained criteria of validation and application,[6,10] we performed a comprehensive review of the validation studies of PROMs for symptomatic PAD. A PubMed search was conducted (B.T.) on January 9, 2020 using a combination of keyword and MeSH terms and updated on December 8, 2020 (Table S2). Editorials, letters, and comments were excluded, as were studies not in English; results provided to the coauthors for review were restricted to the timeframe of January 1, 1995 through December 8, 2020 (Figure S1).

A total of 2198 studies met the inclusion criteria. Abstracts from each study were entered into Covidence, an online screening tool, and were independently screened (J.A.R., D.N., M.C.). Studies with <25 patients, those that did not include patients with symptomatic PAD, and those that were not validation studies were excluded. Studies were included if >50% of patients had claudication; studies with >50% of patients with CLTI were excluded. Any disagreements that occurred between the 2 screeners (J.A.R., D.N.) were adjudicated by the senior author (K.G.S.), who made the final decision.

VALIDATION OF PROMS FOR PAD

A broad range of validation criteria were considered.[7,11] For this review, we used the typical process for questionnaire development following the principles of classical test theory to evaluate the state of validation for PROMs in symptomatic PAD[6,10] and considered meeting these criteria as a continuum of validation. PROMs were assessed to determine if they fulfilled defined criteria for content validity, psychometric properties, and expansion of the validation evidence base for each of the disease-specific measures. We quantified how many studies for each PROM involved or included

various psychometric properties or validation tools. We report the number of PROMs with validation evidence for each of these psychometric properties out of the total number of PROMs as a means to demonstrate the overall body of validation work that exists for each of these PROMs.

Content validity is established through defining domains of the questionnaire by performing a literature review, reviewing existing measures, and soliciting stakeholder input from patients and clinicians (Figure). This input helps establish the content and face validity of the PROM and its domains. To look for evidence of content validity, we searched the published work for documentation of a conceptual framework or domains of the measure and its items studied informed by literature review, patients, providers, and other content experts.

Further testing after the development of the PROM, often beginning with small pilot studies and progressing to larger studies in different settings (inpatient, outpatient, primary care, specialty care), is important for establishing psychometric properties (Figure, Table 1).[12,13] To assess psychometric properties, we documented evidence of construct validity, reliability (including internal consistency and test-retest reliability), and sensitivity (including sensitivity to change). For construct validity, we required a Pearson correlation coefficient (r) of ≥0.45, which is an accepted standard in the literature.[14] For the Cronbach's alpha as a measure of internal consistency, a threshold of 0.80 was considered adequate.[12] For the reliability metrics, we documented the intraclass correlation coefficient (ICC) with values >0.75 indicating good reliability.[13] For sensitivity to change, various criteria can be used and we restricted our abstraction to documenting whether there was evidence of establishing this criterion for the individual instruments. A full explanation of the psychometric properties and validation measures is available in the Appendix in the Supplemental Material.

Once evaluation of the initial stages of validation were completed, we then assessed comparative effectiveness research that used the PROM as an outcome. This included assessing the establishment of the MCID across populations, language and cultural adaptations, and clinical validity by correlating PROMs with clinical indices and future PAD prognostic outcomes (predictive or prognostic validity). For expansion of the validation evidence base, we documented the presence of established MCID criteria, use in comparative effectiveness research, and studies linking the PROM data to predict future clinical outcomes. The MCID is defined as the smallest detectable change in the PRO's change score that would be considered a clinically meaningful change in health status, either as established by patients or clinical anchors. We also documented availability of culturally sensitive translations.

For all of the PROMs reviewed, we summarized information about questionnaire administration, including administration time and mode of administration.

DISEASE-SPECIFIC AND GENERIC PROMS

A total of 2198 studies met the search criteria and were published between January 1, 1995 and December 8, 2020. Of these, 157 (7.1%) were content and psychometric validation studies of PROMs and included > 25 patients (Table S3). Table S4 lists the included disease-specific and generic PROMs and demonstrates the phase of validation work achieved by each PROM.

CONTENT VALIDITY

Both the peripheral artery questionnaire (PAQ)[15] and the vascular quality of life questionnaire (VascuQOL)[16] were developed with patient and clinician input, using a multidimensional framework focused on both physical and emotional health. The PAQ and VascuQOL incorporated a summary score as well as subdomains. Both PROMs allow for a composite summary score to be calculated as well as use of the measure at the subdomain level. During the first stage of development of the PADQOL, 38 patients with symptomatic PAD were interviewed to examine for themes common to their disease state.[17] Additionally, during development of the CSI, 11 patients were interviewed regarding symptom and disease concepts.[18]

PSYCHOMETRIC PROPERTIES

Construct Validity

The construct validity of many of these disease-specific PROMs was validated against generic measures,

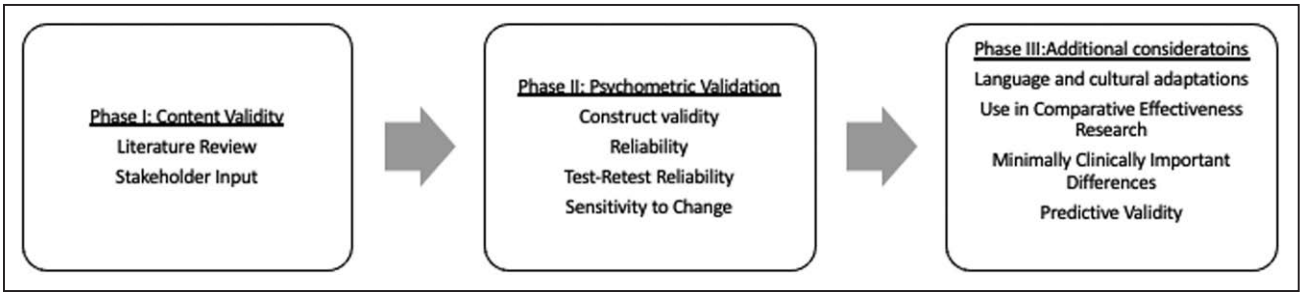

Figure. Stages of development and validation of a patient-reported outcome measure.

Table 1. Definitions of Psychometric Terms or Properties

Domain	Psychometric term/property	Definition
Validity		The degree to which a PROM measures the construct that it intends to measure
	Face validity	Examines whether the tool appears "valid" to the individual being administered the measure or to the personnel administering the measure
	Content validity	Examines whether the content of the PROM (or measure) is a reflection of the construct it intends to measure
	Construct validity	Considers whether the scores produced by the PROM are consistent with how the measure should perform
Reliability		The degree to which the measure is free from measurement error
	Internal consistency	Measures the reproducibility of the measure for different items within a multi-item or multi-domain scale
	Cronbach alpha	Measurement of internal consistency; accepted threshold of alpha >0.80[12]
	Test-retest reliability	Measures the degree to which the score of the measure of a particular patient who has not clinically changed remains the same with repeated measures
	Intraclass correlation coefficient	Measurement of test-retest reliability; ICC with values above 0.75 indicate good reliability[13]
	Recall period	Period of time that a PROM should be readministered again to test test-retest reliability
Responsiveness		Examines the measure's ability to detect changes in a patient over time when there are clinical changes in the construct being measured
	Guyatt responsiveness	An estimate of how responsive a questionnaire is, calculated by the ratio of the mean change score following a treatment and the variance in stable patients, with reported values of 2 or greater constituting larger responsiveness and reference values of 0.2 indicating limited responsiveness
	SRM	The average difference divided by the SD of the differences
	Minimally clinically important difference	Examines the smallest change in the PROM score that reflects changes in the clinical status of the patient

ICC indicates intraclass correlation coefficient; PROM, patient-reported outcome measure; and SRM, standardized response mean

including the commonly used SF-36 and European Quality of Life 5-Dimension (EQ-5D) as well as the walking impairment questionnaire (WIQ),[19–23] a disease specific measure which assesses symptoms, walking ability, walking speed, and stair climbing. The constructs that reached a correlation of >0.45 are listed in Table S3. Other clinical measures applied to correlate commonly used disease-specific PROMs in symptomatic PAD, including the ankle-brachial index, had low correlations.[24–26] Construct validity for the PADQOL was established by examining the relationship between the PADQOL and SF-36, WIQ, and POMS.[17] For WELCH, the construct validity was examined using the treadmill walking distance (moderate positive correlation with the WELCH, ρ=0.59, P<0.001) and the 6-minute walk test performance (strong positive correlation, ρ=0.82, P<0.001).[27] The construct validity of the AUSVIQUOL was examined using the SF-36.[28] A total of 13 out of the 13 disease-specific PROMs reviewed met this criterion.

Reliability

Eight of the 15 disease-specific PROMs had an overall Cronbach's alpha >0.80 or a Cronbach's alpha >0.80 in > 1 domain. The Cronbach's alpha for both the PAQ[15] and VascuQoL[16] overall reached minimum quality standards of values >0.80 for both the subdomains as well as for summary scores.[15,16,29] The Cronbach's alpha for the individual domains of the WIQ (distance, speed, and stair-climbing) ranged from 0.81 to 0.94.[30,31] The Cronbach alpha of the VascuQoL-6 was 0.82; in another analysis, the Cronbach alpha of the VascuQoL-6 was 0.85 before and 0.94 after revascularization.[32] The Cronbach alpha was ≥0.80 for all 5 factors of the PADQOL, except for positive adaptation.[17] The less frequently used CSI had a Cronbach alpha of 0.73,[18] and the AUSVIQUOL had a Cronbach alpha of 0.87.[28] The initial WELCH validation study did not report a Cronbach alpha.[33]

For the test-retest reliability different approaches were used, depending on the recall period of the PROM. The recall period (ie, the time period over which participants/patients were asked to report on their health (ie, over the past week, over the past 4 weeks, etc) for the PAQ and VascuQoL are different, with the PAQ using a 2- to 4-week time period recall while the VascuQoL uses a 1- to 4-week recall.[15,16,34] The PAQ established the test-retest reliability criterion within 2 weeks and obtained ICCs for test-retest scores between 0.70 and 0.90 for the individual domains and summary score.[15] One study reported an ICC of 0.90 for the summary score of the VascuQoL.[16] A 2-week recall period has been used for the WIQ, with ICCs for test-retest scores ranging between 0.68 and 0.83 for the 3 WIQ domains when self-administered and between 0.74 and 0.88 when telephone-administered.[35] Additionally, for the Brazilian-Portuguese version of the VascuQoL-6, the ICC was 0.84 with a 1-week recall period.[36] The lesser used CSI had test-retest reliability measured with an ICC of 0.86.[18] Overall, and considering

the evidence available thus far, metrics for reliability are well established for both the PAQ and VascuQoL, with greater variability reported for the internal consistency results for the WIQ. The PADQOL did not report test-retest reliability.[17]

Sensitivity to Change (Responsiveness)

A total of 6 of 15 PROMs documented sensitivity to change for the PROM. A variety of methods were used, including the Guyatt Responsiveness Index. The Guyatt Responsiveness Index is calculated by the ratio of the mean change score following a treatment and the variance in stable patients, with reported values ≥2 constituting larger responsiveness and reference values of 0.2 indicating limited responsiveness. A Guyatt Responsiveness value of 4.1 was reported for the PAQ.[15,37] The VascuQol used anchor-based approaches to correlate the mean change with global rating of change questions to establish the criterion for sensitivity to change in patients who underwent various treatment approaches for symptomatic PAD as indicated.[16,20] For both the PAQ and VascuQoL, several studies showed that mean change scores changed statistically over time (eg, before and after revascularization),[15,16,38,39] but whether or not these statistically significant changes were also clinically meaningful should be established against validated MCID criteria. The VascuQoL-6 demonstrated excellent responsiveness to change after revascularization with a standard response mean of 1.12.[40] Additionally, the initial validation study of the CSI demonstrated that the CSI total score before and after revascularization correlated significantly with the WIQ distance change score and the change in the total VascuQoL score (both $P<0.05$).[18] The ICQ demonstrated a significant improvement in standard response mean for patients who underwent revascularization.[41] The PADQOL and AUSVIQUOL do not report the responsiveness of the measures to change in disease state.[17,28]

EXPANSION OF VALIDATION EVIDENCE BASE

Use of PROMs in research evaluating the effectiveness of PAD treatments was documented for 3 of the 15 disease-specific measures, whereas 3 of 9 generic measures that were reviewed have been used as secondary end points. A few examples of these registries and trials are listed in Table 2.[42–55] For example, the EUCLID trial included the EQ-5D, VAS, and PAQ,[43] while the CLEVER trial used the SF-12, PAQ, and WIQ.[4] Most commonly, the PAQ and VascuQOL are used (disease-specific), along with the SF-36, SF-12, or EQ-5D (generic) (Table 2).

A total of 4 out of 15 disease-specific PROMs (the PAQ, VascuQoL, VascuQoL-6, and the WIQ) had validated MCID criteria for symptomatic PAD. Both the PAQ and VascuQoL have established MCID.[39,56,57] The PAQ previously used a distribution-based approach and defined it as a medium effect size in an endovascular revascularization cohort; however, more recent efforts also established the MCID using patient-reported patient anchors, with the latter method considered more ideal to represent the patient perspective.[58] The VascuQol used similar patient anchor-based approaches to establish the MCID for improvement and deterioration.[56,57] The MCID of the VascuQoL-6 was defined in a population of patients with intermittent claudication who had undergone revascularization.[38] Finally, a recent analysis estimated the MCID for small, moderate, and large changes in the WIQ distance, speed, and stair-climbing score following 3 months of exercise intervention.[56,59]

A total of 7 out of 15 measures had at least 1 other language translation and validation available. For the VascuQOL, PAQ, and WIQ, myriad translations are available (Table S3), with several of them being published and having undergone dedicated validation work sensitive to the cultural setting of the target language and geographic area of use.[19,30,31,36,60–70] The VascuQol has a 6-item short version of the measure and validation efforts are underway.[32]

Finally, PROMs in PAD are increasingly used to risk-stratify patients and to predict clinical end points relevant to symptomatic PAD. Several PROMs have been studied for the association of change in the PROM with subsequent outcomes.[71–73] In one longitudinal study of 442 participants with PAD, a 20-point decline in the total WIQ score was associated with significantly elevated cardiovascular and all-cause mortality.[74] In another analysis of patients enrolled in the EUCLID trial, the investigators found a significant association between baseline EQ-5D and PAQ scores and adjusted major adverse cardiovascular events, major adverse limb events, and lower extremity revascularization events, as well as a significant association between improvement in EQ-5D and reduced risk of adjusted MACE and lower extremity revascularization event.[72] While the EQ-5D is a generic tool, one analysis of 711 patients with PAD demonstrated that patients with the lowest tertile of EQ-5D score had the highest mortality risk.[71]

ADMINISTRATION

The VascuQOL[16] and the PADQOL[17] require ≈9 minutes to complete and the WIQ[75] takes around 5 minutes to complete when administered by an interviewer[76] and 5 to 10 minutes when self-administered.[48,49] The CSI and ICQ take ≈3 to 4 minutes to complete.[18,41] For the other commonly used disease-specific PROMs, no explicit time durations for completion were reported in studies that we reviewed. Most PROMs could be completed by the patient (self-administered) or an interviewer, with fairly consistent measures by different methods (interviewer versus self-reported), at least as documented for WIQ and EQ-5D.[35,77]

Table 2. Examples of PROMs Used in Recent PAD Clinical Trials and Registries

PAD clinical trial or registry	PROM used
CLEVER trial[4,42]	SF-12, PAQ, WIQ
EUCLID trial[43]	EQ-5D and VAS, PAQ
PORTRAIT registry[25,44,45]	PAQ, EQ-5D, PHQ-8, GAD-7, ENRICHD Social Support Inventory, Perceived Stress Scale, DS14, Problem-Solving Decision-Making Scale, SURE instrument, Medication Discussion Questions
STROLL trial[46]	PAQ, SF-12, EQ-5D, WIQ
ERASE[5]	VascuQOL and SF-36
SMART-PAD[47]	WIQ and SF-36
LITE trial[48]	SF-36 and WIQ
HONOR trial[49]	SF-36, WIQ, PROMIS mobility, pain interference, and role functioning
Randomized controlled trial of orchid drug-coated balloon versus standard percutaneous transluminal angioplasty for treatment of femoropopliteal in-stent restenosis[50]	WIQ and EQ-5D
EffPac Trial[51]	WIQ and EQ-5D
Eximo Medical B-Laser IDE Study[52]	WIQ
OSPREY trial[53]	WIQ
PLAISIR trial[54]	EQ-5D
ILLUMENATE Global Study[55]	EQ-5D and WIQ

CLEVER indicates Claudication: Exercise Versus Endoluminal Revascularization; EffPac, Drug-Coated Balloon Angioplasty of Femoropopliteal Lesions Maintained Superior Efficacy Over Conventional Balloon; ERASE, Endovascular Revascularization and Supervised Exercise; EUCLID, Ticagrelor Versus Clopidogrel in Symptomatic Peripheral Arterial Disease; HONOR, Home-Based Monitored Exercise for PAD; ILLUMENATE, Stellarex Drug-Coated Balloon for Treatment of Femoropopliteal Arterial Disease; LITE, Low Intensity Exercise Intervention in PAD; OSPREY, Occlusive-Stenotic Peripheral Artery Revascularization Study; PAQ, peripheral artery questionnaire; PLAISIR, Femoropopliteal In-Stent Restenosis Repair; PORTRAIT, Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories; SMART-PAD, Sonodynamic Therapy Manipulates Atherosclerosis Regression Trial on Patients With PAD and Claudication; STROLL, S.M.A.R.T Nitinol Self-Expandable Stent in the Treatment of Obstructive Superficial Femoral Artery Disease); and WIQ, walking impairment questionnaire.

GENERIC PROMS USED IN SYMPTOMATIC PAD

The generic PROMs most frequently used in patients with symptomatic PAD are the SF-36[78] and EQ-5D.[79,80] The SF-36 and, to a lesser degree, the EQ-5D have been primarily used as a measure to validate the PAD-specific PROMs, although both have relatively high correlations with PAQ and VascuQOL subdomains and the EQ-5D (both the visual analogue scale and index score) can discriminate between patients' walking distance and has reference values established in patients undergoing endovascular revascularizations and those who are medically managed.[15,16,60,81–85] An analysis of patients undergoing percutaneous transluminal angioplasty demonstrated that SF-36 values significantly increased in patients after percutaneous transluminal angioplasty and exercise.[86] However, other studies showed no change in SF-36 in response to an effective exercise intervention.[42,48,87] Additionally, the SF-36 has been shown to have a moderate-to-good association with several Health Utility Indices and therefore may be useful for economic analyses.[83] Benefits of the EQ-5D include its brevity, ability to generate utility scores to be used in costing analyses, and the universal availability of normative scores globally.[84] These benefits have made the EQ-5D a commonly used measure for end points in comparative effectiveness studies.[25,43–45,51] While the SF-36 offers most of these benefits, the response burden is more significant with 36 items and fewer studies of people with PAD have used its shorter version, the SF-12.[39,88] Both the SF-36 and another shorter version, the SF-8, have undergone validation work in patients with symptomatic PAD.[89] In an analysis comparing the SF-36, EQ-5D, and NHP in a population of patients with lower extremity ischemia, all 3 PROMs had test-retest reliability coefficients >0.7, but the validity of the SF-36 and NHP were higher than the EQ-5D.[90] The SF-36 was also responsive to changes in physical activity, pain, psychological status, and social activity.[90] Other lesser used PROMs, including the MHIQ, have demonstrated significantly lower scores across physical, social, and emotional subdomains in patients with intermittent claudication compared with healthy control.[91]

OTHER DISEASE-SPECIFIC PROMS IN SYMPTOMATIC PAD

PROMs currently in development include the 16-item Intermittent Claudication Questionnaire[41] and the 38-item PADQOL.[17] Other measures have not completed phase I

or early phase II validation, including the Baltimore Activity Scale for Intermittent Claudication.[92]

DISCUSSION

In this review of PROMs in patients with symptomatic PAD but without CLTI, conceptualization, development, operationalization, and validation of disease-specific and generic PROMs were evaluated. The VascuQoL, PAQ, and WIQ are disease-specific measures that have been validated using content and psychometric measures and further expansion of the validation evidence base through the establishment of MCIDs. They have documented differences and change in randomized clinical trials and observational longitudinal cohort studies. Newer PROMs with fewer validation studies performed, mostly restricted to the content validity and psychometric validation stage, are the Intermittent Claudication Questionnaire[41] and the PADQOL.[17] Most disease-specific PROMs used in symptomatic PAD measure multiple aspects of health-quantifying symptoms, functioning (physical, social, mental/emotional), and quality of life, with the exception of the commonly used WIQ, which specifically focuses on symptoms related to walking performance and difficulty with walking specific varying distances, speeds, and climbing more stair flights associated with walking impairment in PAD.[75] It is important to note that while the VascuQoL has a significant amount of validation work, much of the work was in populations that included both people with intermittent claudication and those with CLTI. The other disease-specific measures had validation work performed in populations restricted to intermittent claudication.

Studies of the PAQ and WIQ demonstrated that they had undergone extensive efforts to establish face and content validity using direct input from patients and other stakeholders and correlating them with existing health status measures, such as the SF-36 and EQ-5D, to further establish construct validity. Clinical indices, such as the ankle-brachial index, generally performed poorly to establish construct validity, defined as correlation coefficients <0.45. However, at least one study showed a highly statistically significant association of ABI with the WIQ distances score and speed score.[93] The correlation between ABI, functional capacity and symptom severity in PAD is known to be inconsistent, and thus ABI is just one of many factors to consider.[94]

The PAQ, VascuQOL, and WIQ reached minimum quality standards for internal consistency for both the subdomains and summary scores. These PROMs also provided evidence that they are able to detect meaningful differences between disease states and changes over time in response to treatments for symptomatic PAD. The VascuQOL and PAQ have primarily been used to detect changes following invasive treatment, while the WIQ has been extensively used in randomized trials of invasive treatments, exercise, and medical therapy. MCID criteria for PAQ and VascuQOL were developed using distribution-based approaches and patient anchors. The MCID values for the WIQ used both clinical anchors and distribution-based approaches.[59] A shorter 6-item version of the VascuQOL has been developed, further reducing the patient-response burden.

The commonly used EQ-5D and SF-36 may be the most optimal generic PROMs due to their brevity and use in health economic analyses as well as the availability of norms allowing for use and comparability across cross-cultural settings, languages, and disease populations. The availability of reference values for various symptomatic PAD populations around the world for the EQ-5D and its sensitivity to discriminate between patients with various degrees of lower-extremity disability are advantages, along with its user-friendliness and the ability to derive utilities for cost analyses.[79,80,83] While the SF-36 offers most of these benefits, the longer questionnaire, with 36 items, may be more burdensome to complete. The shorter version, the SF-12,[39,88] is not as widely used.

While there is increasing interest in measuring patient reported outcomes, growing evidence suggests that patient reported outcomes are complementary to objective measures and should not replace objective measures in PAD. For example, in the CLEVER randomized trial that compared endovascular revascularization, supervised treadmill exercise, and medications in 111 participants with symptomatic PAD and aortoiliac disease, supervised treadmill exercise improved treadmill walking distance more than both endovascular revascularization and medications, while endovascular revascularization improved the WIQ and SF-36 more than exercise and the control group, respectively.[4] More recently, the LITE clinical trial randomized 305 participants with PAD to home-based walking exercise at a pace inducing ischemic leg symptoms, home-based walking exercise at a comfortable pace without ischemic leg symptoms, or an attention control group.[48] At 12-month follow-up, home-based walking exercise at a pace inducing ischemic leg symptoms significantly improved 6-minute walk distance more than walking exercise at a pace without ischemic leg symptoms and more than the attention control group. However, each exercise intervention significantly improved the WIQ distance score compared with the control group, and there was no significant difference in change in WIQ distance score between exercise at an intensity inducing ischemic leg symptoms and exercise at a comfortable pace without ischemic leg symptoms.[48] A recent meta-analysis of exercise clinical trials in people with PAD documented significant discrepancies between objective improvement in 6-minute walk distance and participant reported outcomes with regard to improved walking ability after an exercise intervention.[59] Together, these studies underscore the degree to which objective measures and PROMs are complementary and the importance of

measuring both objective and patient reported outcomes for a more complete understanding of the effects of interventions. This issue is important particularly for randomized trials that are not double-blinded.

A substantial part of the validation groundwork for PROMs in symptomatic PAD has been established with measures that have met important validation milestones and a growing comparative effectiveness evidence base comparing PAD treatment effects using both disease-specific and generic PROMs. Currently, there is no single best PROM for clinical practice or PAD trials. It is important to consider the use of multiple PROMs in combination with objective measures, such as walking performance metrics, since clinical trials in PAD have frequently demonstrated variability in outcomes between objective and subjective measures.[4,87,95–97] The use of one measure over another will likely be guided by the research team's preferences and familiarity with the measure, practicality and accessibility, and the nature of the intervention. Investigators should select PROMs that are well-validated and best aligned with the interventions and their anticipated effects. For example, a PROM approach for an exercise intervention that focuses on the lower extremities may place greater emphasis on measures that extensively capture lower-extremity functioning, such as the WIQ, in addition to generic measures that capture broader domains of function.

An important observation of this review is that PROM data are often collected in relatively smaller, siloed efforts. This, in addition to the availability of multiple PROMs, is making it harder to consolidate evidence regarding PROMs in symptomatic PAD. To address this heterogeneity, existing trial and registry data containing PAD health status information should be more widely accessible to researchers in intraacademic collaborative partnerships so that further validation efforts (eg, further definition of MCIDs and meaningful changes in various clinical pathways for PAD treatment, cross-mapping various health status measures, clinical and prognostic validity for relevant PAD clinical end points, etc) can be defined. Beginning in 2023, the NIH will require that investigators make databases publicly available.[98] Finally, it may be helpful to administer PROMs in real-world clinical practice. Further work is needed to determine whether PROMs can be useful in clinical practice for improving outcomes in people with PAD.

This review has several limitations. First, this was not a systematic review, as only PubMed was searched. Some relevant references may have been missed. Second, the review was not registered. Third, the literature was reviewed against a classical test theory framework; alternative interpretative frameworks may offer complementary insights.[7,8] Additionally, the exclusion of non-English studies or reports limit the conclusions of this review. Finally, the quality of the reviewed literature was not assessed.

CONCLUSIONS

In assessing PROMs in patients with symptomatic, non-limb threatening PAD without ischemic rest pain, the PAQ, VascuQOL, WIQ, EQ-5D, and SF-36 have undergone the most thorough validation. Clinicians and scientists should select the PROMs most closely aligned with their scientific and clinical goals, recognizing that there are several validated alternatives to choose from and that outcome measures can be complementary.

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Supplemental Material

Supplemental Methods
Supplemental Results
Tables S1–S4
Figure S1

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