A state-of-the-art review of quality-of-life assessment in venous disease

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ABSTRACT

Objective: Chronic venous disease is a common condition and has a significant impact on patients' health status. Validated patient-reported outcome measures (PROMs) used to assess health status are needed to measure health status. This state-of-the-art review summarizes the current validation evidence for disease-specific PROMs for chronic venous disease and provides a framework for their use in the clinical setting.

Methods: A literature search in OVID Embase and Medline was conducted to identify relevant English-language studies of chronic venous disease that used disease-specific PROMs between January 1, 1993, and June 30, 2022. Abstracts and titles from identified studies were screened by four investigators, and full-text articles were subsequently screened for eligibility. Data on validation of disease-specific PROMs was abstracted from each included article. Classical test theory was used as a framework to examine a priori defined validation criteria for content validity, reliability (construct validity, internal reliability, and test-retest reliability), responsiveness, and expansion of the validation evidence base (use in randomized controlled trials and comparative effectiveness research, cultural or linguistic translations, predictive validity, or establishing the minimal clinically important difference threshold, defined as smallest amount an outcome or measure is perceived as a meaningful change to patients). The PROMs were categorized into three groups based on the manifestations of disease of the population for which they were developed. The overall validity of each PROM was assessed across three stages of validation including content validity (phase 1); construct validity, reliability, and responsiveness (phase 2); and expansion of the validation evidence base (phase 3).

Results: Of 2338 unique studies screened, 112 studies (4.8%) met inclusion criteria. The eight disease-specific PROMs identified were categorized into three groups: (1) overall chronic venous disease (C1 to C6); (2) C1 to C4 disease; and (3) C5 to C6 disease. Assessed by group, the Chronic Venous Insufficiency Questionnaire met criteria for validation at all three phases for patients with C1 to C4 disease, and the Charing Cross Venous Ulcer Questionnaire met criteria for validation at all three phases for patients with C5 to C6 disease. There were no PROMs that met all criteria for validation for use in overall chronic venous disease (C1 to C6).

Conclusions: Of the eight PROMs assessed in this review, only two met prespecified criteria at each phase for validation. The Chronic Venous Insufficiency Questionnaire and Charing Cross Venous Ulcer Questionnaire should be considered for use in patients with chronic venous disease without venous ulcers and with venous ulcers, respectively. (J Vasc Surg Venous Lymphat Disord 2023;■:101725.)

Keywords: Quality of life; Varicose veins; Venous insufficiency; Venous ulcer

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Chronic venous disease (CVD) is a common global condition affecting nearly 60% of the population, with the prevalence expected to increase due to rising rates of obesity and an aging population.[1] The manifestations of CVD are categorized by the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification system.[2] CVD can present as either asymptomatic or symptomatic, with manifestations ranging from telangiectasias or varicose veins (C1 and C2) to edema, skin pigmentation, lipodermatosclerosis, corona phlebectatica (C3 and C4), and healed or active venous ulcers (C5 and C6).[2] Symptomatic CVD can have a significant impact on quality of life and may impose financial burdens on patients and the health care system.[3] Disability from CVD has led to a loss of an estimated 2 million workdays per year and early retirement,[4] and venous leg ulcers alone account for 1% to 2% of total national health care costs.[5,6]

Given the chronic nature of the disease, treatment options have focused on improving patients' quality of life and health status. Patient-reported outcome measures (PROMs), direct measures of health status (physical, mental, functioning, symptoms) obtained by questionnaires, have been used to assess different treatment modalities clinically and in comparative effectiveness research.[7-9] Comparative effectiveness literature for CVD has used PROMs designed to assess patients' overall health (generic PROMs) as well as measures specifically tailored to CVD (disease-specific PROMs), with disease-specific measures having the advantage of greater sensitivity and specificity.[9,10]

Current United States Food and Drug Administration guidelines for industry[11-13] recommend the use of classical test theory, a quantitative approach to testing reliability and validity to develop and validate PROMs. This has allowed for a standardized approach to establishing content validity, reliability (construct validity, internal reliability, and test-retest reliability), and responsiveness, as well as expanding the validation evidence base for PROMs used in a specific therapeutic area. However, there have been limited efforts to systematically evaluate the validity of CVD-specific PROMs within this conceptual framework for CVD. Given this gap, we conducted a state-of-the-art review of disease-specific PROMs using classical test theory framework.

ARTICLE HIGHLIGHTS

- **Type of Research:** State-of-the-art review of disease-specific patient-reported outcome measures in chronic venous disease
- **Key Findings:** The Chronic Venous Insufficiency Questionnaire and the Charing Cross Venous Ulcer Questionnaire were the only patient-reported outcome measures to meet prespecified criteria for validation in patients with chronic venous disease without venous ulcers and patients with venous ulcers, respectively.
- **Take Home Message:** The Chronic Venous Insufficiency Questionnaire and Charing Cross Venous Ulcer Questionnaire should be considered for use in patients with chronic venous disease without venous ulcers and venous ulcers, respectively. Further work is needed to implement these measures into clinical care, such as defining minimal clinically important difference thresholds.

METHODS

Measures of validation of PROMs in CVD. PROMs were judged to have met prespecified criteria for: (1) content validity (how well a measure covers the important aspects of chronic venous disease determined by clinician and/or patient input to derive the conceptual framework and items); (2) psychometric validation (clinical and construct validity ["does the PROM measure what it is intended to measure?"], reliability ["how reliably does the PROM measure the effect of chronic venous disease?"], test-retest reliability ["how reliable is the PROM with repeat testing?"], and responsiveness [can the PROM detect changes over time or with change in clinical status?"]); and (3) expansion of the validation evidence base (use in randomized controlled trials [RCTs] and comparative effectiveness research, cultural or linguistic translations, predictive validity, or establishing the minimal clinically important difference [MCID] threshold, defined as smallest amount an outcome or measure must change to be meaningful to patients) along a three-phase continuum (Fig 1).[14] Features supporting expansion of the evidence base were adapted from Rymer et al.[14] We chose to include features that allowed for PROM use in broader populations, demonstrated routine use of a PROM, or allowed for deeper understanding of PROM score or change in PROM scores. The definitions and a priori determined criteria for validation for content validation, psychometric properties, and expansion of the evidence base are summarized in Table I.[14-21] To allow for potential clinical use and ease of interpretation, PROMs were grouped into three categories based on the manifestations of chronic venous disease for which the PROM was designed (Table II). The groups include: (1) the full spectrum of CVD (C1 to C6); 2) C1 to C4 disease; and (3) C5 and C6 disease. The number of PROMs meeting validation criteria at each phase for each clinical group was documented.

PROM selection and literature review. A literature search was conducted (A.G.) in OVID Embase and Medline using keywords and Medical Subject Headings (MeSH) terms. Full search details can be found in Supplementary Table I (online only). For the purposes of this review, full version and accompanying short-form PROMs that: (1) are disease-specific to CVD; (2) are

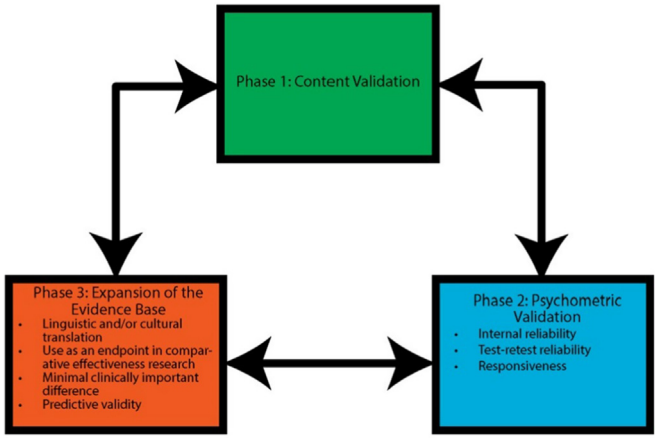

Fig 1. Schematic for the continuum of validation for disease-specific patient-reported outcome measures (PROMs) in chronic venous disease (CVD).

designed for patients with reflux or mixed reflux-obstructive pathology; and (3) use questions that were developed de novo (ie, not built from or adapted from questions on existing generic or disease-specific PROMs) were included. Studies including PROMs of interest were then included if: (4) CEAP classification was documented; and (5) they were conducted between January 1, 1993, and June 30, 2022. We chose to include only patients with reflux pathology or mixed reflux-obstructive pathology, as opposed to reflux, obstructive, and mixed pathology, to assess validation on a homogenous population. Studies were excluded if: (1) patients with concomitant lower extremity peripheral artery disease and lymphedema, as defined by the study, were included; (2) there were <25 patients; (3) there was no validation evidence or the study did not expand the validation evidence base; (4) the study was an editorial, commentary, or letter; or (5) the study was not in English.

Abstracts from studies that met all inclusion and exclusion criteria were entered into Covidence,[22] a standardized, online screening and data extraction tool that highlights discrepancies between reviewers and facilitates the review process. Abstracts and titles were screened for inclusion by four independent reviewers (M.H., R.N., K.X., J.C.), and full text review and abstraction was then conducted on studies that met inclusion and exclusion criteria by each of the reviewers. Any disagreement that occurred between reviewers was adjudicated by a senior author (K.G.S.), who made the final decision.

RESULTS

There were 2338 unique studies that met search criteria, and 112 met eligibility criteria (Fig 2). A total of eight disease-specific PROMs were included (Table II).[23-32] Two PROMs were designed for the full spectrum of CVD (C1 to C6), three PROMs were designed for C1 to C4 disease, and two PROMs were designed for C5 and C6 disease. One PROM (the Freiburg Life Quality Assessment questionnaire [FLQA-V]) was designed for patients with chronic venous insufficiency, defined as C3 to C6 disease, and was included in the C5 to C6 group for this review. An overview of the domains and validation data for each PROM evaluated in this review is provided in Supplementary Table II (online only).

PROMs for patients with the full spectrum of CVD (C1 to C6)

Content validity. The Venous Insufficiency Epidemiological and Economic Study Questionnaire [VEINES-QOL/Sym] and the Assessment of Burden in Chronic Venous Disease Questionnaire [ABC-V] were PROMs designed for patients with the full spectrum of CVD (were developed with patient and clinician stakeholder input).[23,24,26-32] They both contain subdomain scores, with overall composite scores available only for ABC-V. Face validity was established for each PROM by provider review.

Psychometric Properties.

Construct validity. Only the VEINES-QOL/Sym met criteria for construct validity, with the symptom and quality of life domains reaching a correlation >0.45 with components of the Short Form 36 Health Survey (SF-36).[27,33] The construct validity of the ABC-V was validated against another disease-specific PROM, the Specific Quality of Life and Outcome Response-Venous (SQOR-V).[24,25]

Reliability. The VEINES-QOL/Sym reported Cronbach's alpha ≥0.80 for both the symptom and quality of life subdomains in each of five culturally or linguistically different populations (English, French, Italian, French-speaking Belgium, and French-Canadian).[27,33] Internal consistency was not evaluated in initial validation studies for the ABC-V.

The VEINES-QOL/Sym met criteria for test-retest reliability with intraclass correlation (ICC) for both quality of life and symptom scores of the VEINES-QOL/Sym ≥0.75, and the recall period, defined as the time between the initial test and the retest, for the VEINES-QOL/Sym was 14 to 30 days.[33] The ABC-V did not document test-retest reliability.

Responsiveness. There were no PROMs that demonstrated responsiveness to change in symptoms for overall CVD. The VEINES-QOL/Sym documented statistically significant mean change scores in patients who had clinically improved but did not use a generally accepted measure for responsiveness.[27]

Expansion of the evidence base. Only the VEINES-QOL/Sym documented expansion of the evidence base. The VEINES-QOL/Sym has several different cultural and linguistic versions, including English, French, French-Canadian, Dutch, Italian, and Turkish.[27,34-36] Additionally, the VEINES-QOL/Sym has been used as an endpoint in clinical trials, including in an RCT of non-thermal venous ablation vs placebo for varicose veins.[37] The VEINES-QOL/Sym did not document an MCID or predictive validity.

Table I. Definitions of domains and psychometric properties by phase along the three-phase continuum with criteria to establish validity

Phase	Domain	Definition	Criteria to establish validity
Phase I	Face validity	An assessment of whether the PROM appears to be appropriate measure of the construct to the person completing or administering the measure	Documentation of expert consensus.
	Content validity	An assessment of whether the PROM accurately captures the full range of the theoretical concept (in this case, chronic venous disease) it is supposed to be measuring	Demonstration of questionnaire development based on review of literature and input from stakeholders (providers and/or patients).
Phase II	Construct validity	An assessment of whether the PROM accurately measures the construct (as compared to accepted measures)	An overall Pearson correlation coefficient ≥0.45 or a Pearson correlation coefficient ≥0.45 in at least one subdomain when compared with a generic health status measure such as the EQ-5D, factor loading ≥0.4 by confirmatory factor analysis, or Eigenvalues ≥1.0 with exploratory factor analysis.
	Internal consistency	Measures the interrelatedness of items within the entire PROM or within domains of the PROM	Cronbach's alpha ≥0.80 or Cronbach's alpha ≥0.80 in one or more subdomain.
	Test-retest reliability	Measures the reproducibility of the measure over time by administering the same test to the same group of patients after a set interval of time	An intraclass correlation coefficient (ICC) or a Pearson correlation coefficient of ≥0.75.
	Recall period	The time between the initial administration of the PROM and the "retest" for test-retest reliability.	We chose to report recall periods only. Although periods of 7-14 days have traditionally been considered "optimal," the actual optimal recall period is dependent on the condition and severity of disease.
	Responsiveness	The ability of a PROM to detect change over time	We required a documented attempt to establish responsiveness using an effect size or effect size index such as Cohen's d or standardized response mean.
Expansion of evidence base			
	Minimally clinical important difference	The smallest amount an outcome or measure must change to be meaningful to patients	
	Use as an endpoint in randomized clinical trials or comparative effectiveness research	N/A	Documentation of use as an endpoint in a randomized controlled trial or prospective or retrospective comparative effectiveness research.
	Predictive validity	The ability to detect a future outcome (ie, mortality).	Documentation of an association between health status and future outcome.
	Culturally sensitive translation or translation into different language	N/A	Documentation of translation and validation of a measure into different language or cultural setting.

N/A, Not applicable; *PROMs*, patient-reported outcome measures.

Validation at all three phases. None of the PROMs originally designed for assessing health status measures across the full spectrum of CVD (C1 to C6) met criteria for validation at all three phases (Table II). The VEINES-QOL/Sym failed to meet validation at phase 2 (psychometric validation) (Table III), and the ABC-V only met criteria for content validity.

Table II. Disease-specific patient-reported outcome measures (*PROMs*) for chronic venous disease (*CVD*) by Clinical Manifestations, Etiology, Anatomic Distribution, Pathophysiology (*CEAP*) classification clinical manifestation and validation phase

	Symptomatic and asymptomatic non-severe CVD				Severe CVD		Validation phases		
PROM	C1	C2	C3	C4	C5	C6	Phase I (content validation)	Phase II (psychometric validation)	Phase III (expansion of the evidence base)
ABC-V	X	X	X	X	X	X	X		
VEINES-QOL/Sym	X	X	X	X	X	X	X		X
CIVIQ	X	X	X	X			X	X	X
AVVQ	X	X	X	X			X		X
SQOR-V	X	X	X	X			X		
FLQA-V			X	X	X	X	X		
CCVUQ					X	X	X	X	X
VLU-QoL					X	X	X		X

ABC-V, Assessment of Burden in Chronic Venous Disease Questionnaire; *AVVQ*, Aberdeen Varicose Vein Questionnaire; *CCVUQ*, Charing Cross Venous Ulcer Questionnaire; *CIVIQ*, Chronic Venous Insufficiency Questionnaire; *FLQA-V*, Freiburg Life Quality Assessment-Venous; *SQOR-V*, Specific Quality of Life and Outcome-Venous; *VEINES-QOL/Sym*, Venous Insufficiency Epidemiological and Economic Study Questionnaire; *VLU-QoL*, Venous Leg Ulcer Quality of Life.

PROMs for patients with C1 to C4 disease

Content validity. The Aberdeen Varicose Vein Questionnaire (AVVQ) as well as the Chronic Venous Insufficiency Questionnaire (CIVIQ) questionnaires were developed with both patient and clinician stakeholder input and met criteria for face validity as determined by expert consensus. The Specific Quality of Life and Outcome Response-Venous (SQOR-V) only used clinician input.[25] All PROMs provide subdomain scores as well as composite scores.

A short-form questionnaire with 14 items, CIVIQ-14, was developed for the CIVIQ-20.[28]

Psychometric Properties.

Construct validity. Both the CIVIQ questionnaires and the AVVQ met criteria for construct validity. Construct validity for the CIVIQ-20 was initially investigated using factorial analysis, with instability noted in the Social subdomain[29,38]; however, the CIVIQ-14 demonstrated a stable construct by factorial analysis and strongly correlated ($r = 0.70$) with the EuroQoL-5D (EQ-5D), a generic health status PROM, after elimination of 6 unstable items.[39] The AVVQ was validated against the EQ-5D with a correlation coefficient >0.45.[39] The construct validity of the SQOR-V was investigated against the 12-Item Short Form Survey (SF-12) but noted only trends with no formal testing of correlation, and therefore did not meet criteria for construct validity.[25]

Reliability. The Cronbach's alpha met minimum quality standards of ≥ 0.80 in only one subdomain for CIVIQ-20 (Psychological),[29] but the CIVIQ-14 reported ICC ≥ 0.85 for all subdomains.[40] The AVVQ reported an overall Cronbach's alpha of 0.72 to 0.74 and did not meet criteria for internal reliability.[23,30] An overall Cronbach's alpha of 0.96 was documented for the SQOR-V.[25]

The CIVIQ-20 and CIVIQ-14 both demonstrated test-retest reliability, with an ICC ≥ 0.75 for all subdomains and weighted kappa ≥ 0.8, showing near perfect agreement, for all subdomains, respectively.[28,29] The test-retest recall period for the CIVIQ-20 and CIVIQ-14 was 14 days. The AVVQ documented an ICC of 0.79 and a recall period of 14 days.[41] The SQOR-V had an ICC of 0.79 and a median recall period of 30 days.[25] The ABC-V did not document test-retest reliability.

Responsiveness. Both the CIVIQ questionnaires and the AVVQ demonstrated responsiveness. The CIVIQ-20 reported an overall standardized response mean (SRM) of 1.31, and both the CIVIQ-20 and CIVIQ-14 reported effect sizes ranging from 0.95 to 1.07 after medical therapy.[28,29] The AVVQ demonstrated good responsiveness with a SRM of 0.84 for patients who underwent surgery for varicose veins.[41] We did not find any studies that documented responsiveness for the SQOR-V.

Expansion of the evidence base. Both the CIVIQ and the AVVQ documented expansion of the validation evidence base. The CIVIQ-20 and its short-form are available in over 20 languages and have undergone cultural translation for use in more than 30 countries. We identified 16 RCTs and two prospective comparative effectiveness cohort studies that used CIVIQ-20 or CIVIQ-14 as a clinical endpoint.[37,42-64] The AVVQ has had similar global exposure, with translation into multiple languages, including Portuguese, Hungarian, and Dutch, as

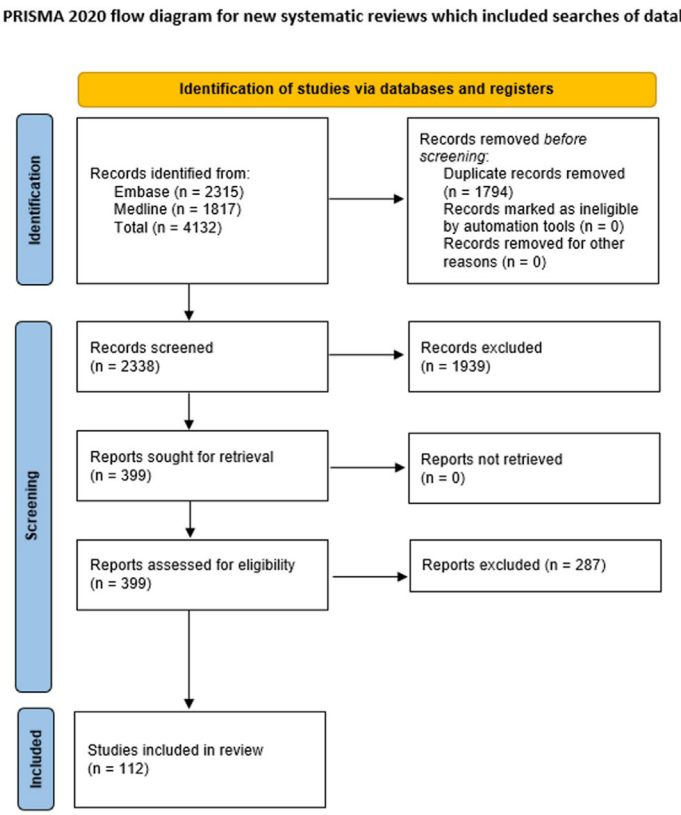

Fig 2. Cohort flow for chronic venous disease (CVD) studies. *PRISMA*, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Table III. Validation of patient-reported outcome measures (*PROMs*) for each of the psychometric properties and components of evidence base expansion

	Phase II				Phase III			
PROM	Construct validity	Internal consistency	Test-retest reliability	Responsiveness	Language & cultural adaptations	Use in comparative effectiveness research	Predictive validity	MCIDs
PROMs for the full spectrum of CVD								
ABC-V					X			
VEINES-QOL/Sym	X	X	X		X	X		
PROMs for non-severe CVD								
CIVIQ-20/ CIVIQ-14	X	X	X	X	X	X		
AVVQ	X		X	X	X	X		
SQOR-V		X	X					
PROMs for severe CVD								
FLQA-V	X	X	X					
CCVUQ	X	X	X	X	X	X		
VLU-QoL	X	X	X		X			X

ABC-V, Assessment of Burden in Chronic Venous Disease Questionnaire; *AVVQ*, Aberdeen Varicose Vein Questionnaire; *CCVUQ*, Charing Cross Venous Ulcer Questionnaire; *CIVIQ*, Chronic Venous Insufficiency Questionnaire; *CVD*, chronic venous disease; *FLQA*, Freiburg Life Quality Assessment-Venous; *MCIDs*, minimally clinical important differences; *SQOR-V*, Specific Quality of Life and Outcome-Venous; *VEINES-QOL/Sym*, Venous Insufficiency Epidemiological and Economic Study Questionnaire; *VLU-QoL*, Venous Leg Ulcer Quality of Life.

well as multiple cultural adaptations.[65-67] We identified 31 RCTs and five comparative effectiveness cohort studies.[7-9,59,68-100] There is no documented MCID or predictive validation for either PROM. We did not find any evidence of expansion of the validation evidence base for the SQOR-V.

Validation at all three phases. Only the CIVIQ questionnaires met criteria for validation at all three phases (Table II). The AVVQ and SQOR-V did not meet all validation criteria for psychometric validation (Table III).

PROMs for C5 and C6 CVD

Content validity. All three PROMs in this group (Freiburg Life Quality Assessment-Venous [FLQA-V], Venous Leg Ulcer Quality of Life [VLU-QoL], and Charing Cross Venous Ulcer Questionnaire [CCVUQ]) met criteria for content validity, as they were developed with both patient and clinician input. Subdomain and composite scores are provided for each PROM. PROMs met criteria for face validity as determined by experts. A 10-item short-form questionnaire was developed for the FLQA-V.[101]

Psychometric Properties.

Construct validity. The VLU-QoL correlated well with the SF-36 with two of the three subdomains having correlation coefficients >0.45.[26] The CCVUQ was validated against the SF-36, and correlation coefficients were >0.45 for all SF-36 subdomains.[31] The FLQA-V was validated against the NHP subdomains with correlations ≥0.45 in most subdomains.[32]

Reliability. The VLU-QoL reported a Cronbach's alpha ≥0.8 for each subdomain, and the CCVUQ reported an overall Cronbach's alpha of 0.93.[26,31] The FLQA-V reported Cronbach's alpha ≥0.8 in six of seven subdomains.[32]

All three PROMs met criteria for test-retest reliability. The CCVUQ documented a correlation coefficient of 0.84 and a recall period of 2 weeks for all subdomains.[31] The ICC of the VLU-QoL was ≥0.75, with a recall period of 2 to 3 days.[26] An ICC of ≥0.75 for five of seven subdomains was documented for the FLQA-V. The recall period was 30 days.[32]

Responsiveness. The CCVUQ documented good responsiveness with an SRM of 0.92 overall (0.62-0.78 for domains).[102] The VLU-QoL and FLQA-V reported a statistically significant linear trend between decreasing symptoms and improving global scores and mean change scores after intervention, respectively, but neither PROM documented an effect size or effect size index.[26,103]

Expansion of the validation evidence base. The CCVUQ has been used infrequently as an endpoint in comparative effectiveness literature[104-106] but did have cultural and linguistic translations.[107] The CCVUQ has no documented MCID or predictive validation. The VLU-QoL has not been used as a clinical endpoint in comparative effectiveness literature and has no available translations. However, the VLU-QoL was the only PROM evaluated to report an MCID.[26] We did not find any studies that expanded the validation evidence base for the FLQA-V.

Validation at all three phases. Only the CCVUQ met criteria for validation at all three phases (Table II). The VLU-QoL did not meet criteria for each psychometric component (phase 2) (Table III). The FLQA-V only met criteria for content validity (phase 1).

DISCUSSION

In this review, validation of eight disease-specific PROMs for CVD was evaluated within three different clinical populations along a three-phase continuum using classical test theory. For overall CVD (C1 to C6 disease), C1 to C4 disease, and C5 to C6 disease, all PROMs demonstrated content validity (phase 1). Only the CIVIQ questionnaires (C1 to C4 disease) and the CCVUQ (C5 to C6 disease) met all a priori determined criteria for psychometric validation (phase 2) and expansion of the evidence base (phase 3). Based on the current evaluation, the CIVIQ questionnaires, and preferably the CIVIQ-14, should be preferentially used in patients with C1 to C4 CVD, and the CCVUQ should be preferentially used in patients with CVD and venous ulcers (C5 to C6) for current and future work, although further validation work on PROMs that did not meet specific thresholds in this review may expand the pool of available well-validated PROMs.

Our work builds upon prior reviews of PROMs in CVD[108-111] by providing a complete overview of PROMs, grouped and assessed by the population for which each PROM was designed. Prior work has concentrated on PROMs for venous ulcers only,[109] did not assess psychometric properties,[111] or simply identified studies that had documented psychometric or other validation evidence without defining or suggesting whether this evidence met quality thresholds for validation.[108,110] The grouping by manifestation in our study provides a framework for use of PROMs in clinical practice. We additionally reviewed PROMs along a three-phase continuum that allows for sequential assessment of validation that mirrors the recommended development process. This framework provides a means for systematic evaluation and identification of gaps in validation along the development pathway for specific PROMs which can inform future studies and quality improvement in PROM development.

Recently, there has been a shift towards value-based and patient-centered care, especially in the management of chronic diseases such as CVD. Well-researched measures of impact and quality of care, such as PROMs, are central to that shift, but have not been implemented in routine clinical care for CVD. In other specialties, however, PROMs have not only been employed in clinical practice, but used as performance metrics (patient-reported outcome-based performance

measures or PRO-PMs), with the goal of establishing benchmarks for quality standards to decrease variability in care.[112] A framework for the development of PRO-PMs developed by the National Quality Forum identified selection of well-validated PROMs as a key component.[113] In addition to rigorous validation, however, it is equally important that the right PROM is chosen for the right patient or patient population. The PROMs designed for the full spectrum of CVD, such as VEINES-QOL/Sym, are more "generic" by design and are less likely to be clinically useful for evaluation of individual patients or subsets of patients with CVD. Although PROMs for C1-C4 disease are more specific, these measures are uniformly applied to patients with telangiectasias (C1 disease) and symptomatic edema (C3) or lipodermatosclerosis (C4). As an example, random sampling of patients from the RELIEF trial[114] was used in the development of the CIVIQ-14 questionnaire. The CIVIQ-14 questionnaire is designed for patients with C1 to C4 disease, but only 12% of patients in the RELIEF trial had C4 disease. This may lead to some limitations to the accuracy of the measure for patients with lipodermatosclerosis, and the development of more specific measures may be indicated in this population, especially as we move towards value-based care in CVD.

Before implementation of PROMs into clinical practice can be realized and the shift to value-based, patient-centered care can occur for CVD, further validation work on PROMs is necessary. First, uniform criteria for establishing psychometric properties should be adopted. Cronbach's alpha was almost uniformly used when assessing for internal consistency; however, a variety of statistical parameters were used for test-retest reliability and responsiveness. We recommend using intraclass correlation for test-retest reliability and an effect size or effect size index for responsiveness after intervention. Second, MCIDs need to be established for PROMs prior to clinical use. PROMs that were shown to meet criteria for responsiveness, such as the CIVIQ questionnaires, can detect change over time in response to an intervention but in the absence of an established MCID it remains unclear if this change is clinically meaningful to patients. Third, predictive validity for "hard" endpoints such as hospitalization or healing of a venous ulcer for PROMs in CVD should be established and may serve as early indicators for the need for intervention. Lastly, the practicality of use in real-world populations must be established for many of the PROMs assessed in this review, including both PROMs that met all a priori defined criteria for validation. For example, of the eight PROMs assessed, only the AVVQ documented the time required to complete the measure (<5 minutes) in studies evaluated for this review.[30] These PROMs can be completed with clinician supervision or independently by patients, as PROMs such as the CIVIQ include instructions for answering the questionnaire. As technology has advanced and internet access has expanded, there is potential for PROMs to be administered electronically.

Limitations. This review has several limitations. First, this was not a systematic review as only the OVID Embase and Medline databases were searched, and relevant validation work may have been missed. Second, the scope of this review was limited to CVD due to reflux or mixed pathology. More extensive validation efforts may have been undertaken in patients with secondary pathology (ie, CVD due to deep venous thrombosis or May-Thurner syndrome) uniquely qualifying some PROMs for use in other specific populations. Third, generic PROMs were not included in the current review, and as such, this review does not capture the holistic view of health status measures in CVD. Fourth, we used a classical test theory framework, and alternative frameworks may provide additional insights. Fifth, definitions of peripheral artery disease and lymphedema were specified by each individual study, allowing for some heterogeneity in the exclusion criteria of concomitant peripheral artery disease or lymphedema. We also acknowledge that there may be undiagnosed or unmentioned lymphatic or peripheral artery disease in the studies reviewed. Lastly, we only considered PROMs that developed questions de novo with input from experts and patients. Newer disease-specific PROMs focused on symptomatic disease, such as the VVSymQ, which were developed from a sample of the VEINES-QOL/Sym items were therefore not included.

CONCLUSIONS

In a review of disease-specific PROMs for chronic venous disease, only two of eight PROMs assessed met prespecified minimum quality standards for validation along a three-phase continuum. For patients with C1 to C4 disease, the CIVIQ-20 and its associated short form CIVIQ-14 met criteria for validation and should be considered for use. For patients with C5 to C6 CVD, the CCVUQ met validation criteria and should be considered for use in patients with venous ulcers. Further validation work is necessary and includes adopting standardized parameters for psychometric validation, establishing minimal clinically important differences, and evaluating for the predictive validity for existing PROMs in CVD.

AUTHOR CONTRIBUTIONS

Conception and design: JC, CM, KS
Analysis and interpretation: JC, KX, GR, RA, AG, CM, KS
Data collection: JC, KX, MH, RN, LS, GR, RA, AG, CM, KS
Writing the article: JC

Critical revision of the article: JC, KX, MH, RN, LS, GR, RA, AG, CM, KS
Final approval of the article: JC, KX, MH, RN, LS, GR, RA, AG, CM, KS
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Overall responsibility: JC

DISCLOSURES

C.M.-H. reports unrestricted research grants from Philips and Shockwave and is a consultant for Abbott Vascular, Cook, Medtronic, and Optum Labs. K.G.S. reports unrestricted research grants from Philips, Merck, Shockwave, and Johnson & Johnson; is a consultant for Optum Labs, Cook, Tegus, Twill Inc, and Abbott Vascular.

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Additional material for this article may be found online at www.jvsvenous.org.

Supplementary Table I (online only). Literature search details in OVID Embase and Medline

Ovid Embase	
1	exp vein insufficiency/
2	varicos*.tw,kw
3	((venous or vein) adj3 (disease* or insufficien* or disorder* or dysfunction* or ulcer*)).tw,kw.
4	1 or 2 or 3
5	patient satisfaction/
6	exp patient-reported outcome/
7	self report/
8	exp perception/
9	attitude to health/
10	((patient-report* or patient report* or self-report* or selfreport* or self report* or self-assess*) adj3 (outcome* or measure* or evaluation*)).tw,kw
11	(PROM or PROMs or PROMIS or PRO measure*).ti,ab
12	(consumer attitude* or patient outcome* or patient report* or patients report* or perception* or self concept*).tw,kw.
13	(patient adj3 satisfaction*).tw,kw
14	exp "quality of life"/
15	(health adj3 (quality-of-life or life-quality)).tw,kw.
16	(HRQL or HRQOL).ti,ab.
17	or/5-16
18	4 and 17
19	exp animal/
20	exp animal/and exp human/
21	19 not 20
22	18 not 21
23	limit 22 to english language
24	limit 23 to yr="1993-current"
25	limit 24 to conference abstracts
26	24 not 25
Ovid Medline	
1	exp varicose veins/or exp venous insufficiency/
2	varicos*.tw,kf
3	((venous or vein) adj3 (disease* or insufficien* or disorder* or dysfunction* or ulcer*)).tw,kf.
4	1 or 2 or 3
5	Patient Satisfaction/
6	exp Patient Reported Outcome Measures/
7	Self Report/
8	exp Perception/
9	exp Attitude to Health/
10	((patient-report* or patient report* or self-report* or selfreport* or self report* or self-assess*) adj3 (outcome* or measure* or evaluation*)).tw,kf.
11	(PROM or PROMs or PROMIS or PRO measure*).ti,ab
12	(consumer attitude* or patient outcome* or patient report* or patients report* or perception* or self concept*).tw,kf
13	(patient adj3 satisfaction*).tw,kf
14	"Quality of Life"/
15	(health adj3 (quality-of-life or life-quality)).tw,kf
16	(HRQL or HRQOL).ti,ab
17	or/5-16
18	4 and 17
19	exp animals/
20	exp animals/and exp humans/
21	19 not 20
22	18 not 21
23	limit 22 to english language
24	limit 23 to yr="1993 -Current"

(Continued)

Supplementary Table II (online only). Overview of patient-reported outcome measure (*PROM*) domains, psychometric properties, and expansion of the evidence base

	Conceptual framework/domain	Content validity	Construct validity	Face validity	Internal consistency	Test-retest	Responsiveness	Cultural/ linguistic translations	Comparative effectiveness	Composite and subscales	Short form
AVVQ	Pain or functional, appearance, severity, complications	Based on common clinical questions and review of literature and patient interviews. Independently reviewed by 2 consulting surgeons. (Garratt)	r >0.45 (0.49) only for physical function (Garratt); r = 0.5 for EQ-5D r = 0.584 with VCSS r = 0.326 with CEAP	Expert opinion	0.72-0.74	ICC = 0.79 (recall period 2 weeks)	SRM 0.84 for patients receiving surgery	Many	Yes- 31 RCT and 5 observational studies.	Yes	No
ABC-V	6 domains- pain, daily life, family and personal relationships, work, treatment by GP, psychological impact	Semi structured interviews with patients and literature review to establish question bank (66 items). Narrowed to 36 based on clinician input	r = 0.806 with SQOR-V	Expert opinion	Not assessed	Not assessed	Not assessed	Many	No	Yes	No
CIVIQ-20	4 domains- pain, physical, psychological, and social	Semi-structured interviews conducted on 20 patients. Interview guide derived from review of literature and interviews with specialists. Complaints assessed by thematic analysis on a multidimensional framework (signs/ symptoms, functional repercussions, psychological impact, social consequences, perception of general health).	PCA and PAF (CFA)-> minor instability with two questions in wrong category (higher loads)	Expert opinion and high patient response in clinical trial (1%-3.9% nonresponse for each item except for 1 which had >19%)	0.853 for psychological, 0.711 for physical; 0.778 for pain, 0.654 for social)	r = 0.8529-0.9774 for each domain; r = 0.9512-0.9803 overall (retest day 15)	SRM 1.31 overall; Domains 0.91-1.28; ES 1.17 overall, 0.80-1.20 for domains. Clinical condition had improved after 2 months	Many	Yes- 16 RCTs, 2 observational	Yes	Yes- CIVIQ-14
CIVIQ-20			Lack of stability in social: convergent validity good across board (100%) but discriminating validity 67% for social, 75% for pain (using multi-trait/ multi-item analysis). Factor loading bad for social- <40 for 2 item out of 3 for social. 1/4 items for physical 2/9 items for psychological		C = 0.94 global; 0.86 for physical, 0.89 for psychological, 0.83 for pain, and 0.76 for social	ICC = 0.956 (global score)	Clinical improvement at 180 days (improvement in swelling, heaviness, cramps, pain): overall d = 1.24-1.46				
CIVIQ-14	3 domains- physical/ social, psychological, pain	Bootstrap samples from RELIEF and removed instability. Combined social and physical subdomains.	r = 0.37-0.51 for total with VCSS Pain r = 0.35-0.52 Physical r = 0.27-0.40 Psychological r = 0.26-0.33 Factorial analysis (two unstable items)		ICC = 0.88	Weighted kappa 0.81-0.87 (15 days)	d (total) = 0.95-1.07 (for various symptoms) Pain d = 1.31-1.47 physical d= 0.81-0.93 Psychological d= 0.61-0.69				
CIVIQ-14			EFA and CFA- CFA showed 3D model better than 2D model. Multi-trait/ multi-item analysis showed good concordance between items and their assigned dimension. r = 0.7 with Eq5d		Cronbach 0.85 pain, 0.92 physical, 0.88 psychological						
CCVUQ	4 domains- social interaction, cosmesis, domestic activities, and emotional status	Patient interviews, literature review, clinician interviews to generate question bank.	EFA and CFA- CFA with all loading >0.4 for respective dimensions. R= 0.333-0.698 when compared to SF-36 (all subdomains compared independently). All subdomains had correlation >0.45 for at least one subdomain of SF-36 overall r = 0.522-0.706 with SF-36 domains	Expert opinion (reviewed by 2 vascular surgeons)	Cronbach 0.93	r = 0.84 (14 days)	Mean score decreased 10% at 6 weeks and 54% at 12 weeks in those who had an active ulcer that healed.	Yes but few- Chinese, Brazil	Yes but very few	Yes	No

Supplementary Table II (online only). Continued.

	Conceptual framework/domain	Content validity	Construct validity	Face validity	Internal consistency	Test-retest	Responsiveness	Cultural/ linguistic translations	Comparative effectiveness	Composite and subscales	Short form
							SRM 0.73 for social function, 0.62 for domestic, 0.68 for cosmesis, 0.78 for emotion, 0.92 overall (12 weeks)- length of time OK given that it takes a long time for uclers to heal.				
FLQA	7 domains- Physical complaints, daily life, social life, emotional well-being, therapy of the venous disease, satisfaction, occupation.	Interview with patients and clinicians. Questions supplemented by general QoL questions from generic PROMs	All subdomains except for "Occupation" r >0.45 for at least one subdomain of the NHP	Expert opinion	Cronbach 0.78-0.92 for each domain (only social life is below 0.8)	r = 0.60-0.84 (social life, therapy, and occupation below 0.75) (time = 1 month)	Mean score change significant for all domains except therapy and social life after 3 months	No	No	Yes	Yes- FLQA-V10
SQOR-V	5 domains- discomfort, appearance, restriction of movements, risk, emotional problems.	Clinician expert opinion and lit review	Not rigorous- compared with SF-12 but compared scores of SQOR with physical and mental components of >50 and <50. No correlation calculated. Did same with CEAP- compared C1-C2 to C3-C6 but did not provide correlation.	Expert opinion	Overall Cronbach 0.96	ICC = 0.79 (median 30 days)		No	No	Yes	No
VEINES-QOL/ Sym	2 domains- quality of life and symptoms	Interviews with patients, clinicians, literature review	Sym: r = 0.34-0.65 with SF -36 PCS; r = 0.15-0.42 with MCS QoL: r = 52-0.73 with PCS; r = 0.19-0.55 with MCS	Expert opinion	Sym- Cronbach 0.82-0.87 (14 day and 30 day) QoL- 0.88-0.94 Depends on language that was validated (simultaneously validated on English, French, Italian as well French-Canadian, French-speaking Belgium)	Sym- ICC 0.75 QoL 0.80 Recall period 2 weeks	Sym r = 1.66 QoL r = 1.44 with clinical improvement at end of study (12 months)	Yes- initially validated in 4 languages- French, Italian, English (Canada), French (Canada), Belgium (French)- then Turkish, Dutch, Portugese/ Brazil, Sweish	Yes but few. Several small single center RCTs. Some small observational studies.	Yes- composite only though (as QoL and Symptoms)	No
VLU-QoL	3 domains- Activities, Psychological, Symptom Distress	Clinician input and interviews with patients. Then adapted questions from SKINDEX-29	PFA analysis; loading >0.4 for all items on respective domains Activities- r = 0.642 for PCS and 0.293 for MCS Psych- r = 0.391 for PCS and 0.462 for MCS Symptom- r = 0.413 for PCS and 0.4 for MCS	Expert opinion	Cronbach >0.8 for all domains	ICC 0.85 for Activities, 0.83 psychological, 0.86 for symptom distress (at 2-3 days)	Evaluated linear trend based on improvement in symptoms and bother- "correlated" for all subdomains	No	No	Yes- Global symptom severity score and "bother" score	No

ABC-V, Assessment of Burden in Chronic Venous Disease Questionnaire; *AVVQ*, Aberdeen Varicose Vein Questionnaire; *CCVUQ*, Charing Cross Venous Ulcer Questionnaire; *CFA*, confirmatory factor analysis; *CIVIQ*, Chronic Venous Insufficiency Questionnaire; *EFA*, exploratory factor analysis; *EQ-5D*, EuroQoL-5D; *FLQA*, Freiburg Life Quality Assessment-Venous; *ICC*, intraclass correlation coefficient; *MCS*, Mental Component Summary (of SF-36); *PAF*, principal axis factoring; *PCA*, principal component analysis; *PCS*, Physical Component Summary (of SF-36); *RCT*, randomized controlled trial; *SF-12*, 12-item Short Form Survey; *SF-36*, 36-item Short Form Survey; *SQOR-V*, Specific Quality of Life and Outcome-Venous; *SRM*, standardized response mean; *QoL*, quality of life; *VCS*, Venous Clinical Severity Score; *VEINES-QOL/Sym*, Venous Insufficiency Epidemiological and Economic Study Questionnaire; *VLU-QoL*, Venous Leg Ulcer Quality of Life.