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Methods of symptom evaluation and their impact on peripheral artery disease (PAD) symptom prevalence: A review

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Abstract

Peripheral artery disease (PAD) is a common progressive atherosclerotic occlusive disease that causes insufficient blood flow to the lower extremities. The symptom that health care professionals most often associate with PAD is claudication. However, patient reporting of claudication is highly variable. A structured literature review was conducted to evaluate how PAD symptoms are identified, defined, and categorized. This review focuses on the development and performance characteristics of PAD symptom questionnaires and the identification of a spectrum of leg symptoms beyond classic claudication. Additionally, potential confounders of PAD symptom report and strategies for a more comprehensive assessment of PAD symptoms are discussed. Overall, there is a lack of consistency in the utilization of PAD claudication questionnaires which impacts PAD symptom reporting and categorization. Based on this review, atypical symptoms are commonly reported, but poorly understood. Additional research is needed to gain a better understanding of the presentation of atypical symptoms, as well as the role of age, gender, race, and comorbid conditions on the symptom experience of patients with PAD.

Peripheral artery disease (PAD) is a progressive atherosclerotic occlusive disease that causes insufficient blood flow to the lower extremities and can result in debilitating, activity-induced, pain even while walking short distances. Estimates vary widely, but currently it is estimated that over 8 million Americans are afflicted with PAD.[1–3] The prevalence has been shown to increase with age, particularly in individuals aged 60 years and older.[4,5] Therefore, as the population ages, PAD will become increasingly prevalent. Despite the high prevalence of PAD, it remains largely underdiagnosed and undertreated.[2,6] Evidence suggests the underutilization of inexpensive and widely available diagnostic screening tools,[7] guideline-recommended treatments,[8] and lifestyle modifications.[8] Early detection of PAD is crucial for timely treatment and prevention of amputation, heart attack, stroke, and death.[9–12] Individuals with PAD have 4 to 5 times the risk of dying of a cardiovascular event compared to those without PAD, which translates into a mortality risk that is 2 to 3 times higher.[13,14]

The presentation and progression of PAD is varied. Some individuals remain asymptomatic despite disease progression, while others consistently experience discomfort upon exertion that subsides when activity ceases. Critical limb ischemia (CLI) is the most severe form of PAD. Individuals with CLI typically experience severe leg pain even while resting that usually occurs in the feet or toes. However, for some individuals with CLI, the first sign of the disease is the presence of tissue loss.[15] In patients with CLI, blood flow to the lower extremities is severely reduced, resulting in chronic non-healing wounds and tissue necrosis that if left untreated can lead to amputation.

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PAD symptoms have been assessed through a series of questionnaires that have evolved over time.[16–18] Of the symptoms reported by individuals with PAD, the symptom that health care professionals most often associate with the disease is claudication, also referred to as classic claudication, Rose intermittent claudication (Rose IC), intermittent claudication (IC), or definite claudication.[16] This has been classically defined as a painful, aching, cramping, or tired feeling in the calves that occurs during walking, does not begin at rest, does not subside if walking continues, and is relieved within 10 minutes or less when activity ceases. In this paper, this specific symptom presentation will be referred to as *classic claudication*. It is the PAD symptom that usually triggers confirmatory diagnostic testing,[19] most commonly the ankle-brachial index (ABI), which is the ratio of systolic ankle versus brachial pressure.

Classic claudication, as measured by a variety of questionnaires, is only reported in 7.5%[20] to 33%[18,21,22] of PAD patients. Thus, heavy reliance on this symptom for screening and detection can result in mis- or under-diagnosis of this serious disease. This under-diagnosis allows the disease to progress undetected, leading to increased morbidity and mortality. In order to increase accurate and timely diagnosis and clinical treatment for the more than 8 million Americans afflicted with PAD, it is necessary to gain a greater understanding of the array of symptoms experienced, including not only classic claudication, but other symptoms that are currently considered an atypical presentation of the disease.

This review critically evaluates how PAD symptoms are identified, defined, and categorized. It focuses on the development and performance characteristics of PAD symptom questionnaires and the identification of a spectrum of leg symptoms beyond classic claudication. Additionally, potential confounders of PAD symptom report and strategies for a more comprehensive assessment of PAD symptoms are discussed.

Methods

Four electronic databases were used for this review: CINAHL, MEDLINE, The Cochrane Library, and Digital Dissertations, utilizing the following keywords: *peripheral vascular disease, peripheral artery disease, atherosclerosis, diagnosis, recognition, ankle-brachial index, questionnaires, experience, symptom(s), prevalence, atypical, claudication, intermittent claudication, pain,* and *asymptomatic*. Limits included English language, humans, and adults. No date limits were set and electronic searches were supplemented by cross-referencing. Only empirical studies describing the breakdown of symptom reporting into multiple categories beyond classic claudication prevalence (e.g. Rose claudication and atypical claudication) were included, with the exception of the first claudication questionnaire developed.[16] Studies focused solely on PAD prevalence, classic claudication prevalence, quality of life, or asymptomatic disease were excluded. Symptom confounders were of interest, but were not part of the inclusion and exclusion criteria.

A total of 584 papers were examined. After reviewing the full text of 93 articles, 32 met the inclusion criteria of the review (see Table 1). The literature review search process, including the reasons for exclusion at each stage of screening is presented in Figure 1. The 32 papers included in the review were evaluated in ascending chronological order using a structured abstracting form with eleven topics: first author, year of publication, sample size, mean age/ age range, gender, mean ABI, study selection criteria, symptom tool, sensitivity, specificity, and symptom prevalence. Limitations of this review include using English language as a search restriction, thus not including articles published in other languages. Additionally, not including papers and reports unpublished in journals, such as conference abstracts and presentations, may have limited the comprehensiveness of the review.

Results

The results of the structured evaluation are presented in Table 1. The papers included in the review are also denoted with an asterisk in the reference list. Sample sizes ranged from 20[23] to 6,417[2] participants, with an average of 1,197 participants. Research designs were mostly cross-sectional, but qualitative results were also included.[23,24] In instances where population characteristics were only listed for subgroups, the numbers reported for the entire sample were calculated based on the information reported.

PAD Symptom Questionnaires

Symptom assessment often involves a combination approach: an oral report of symptoms to a provider and written completion of a PAD symptom questionnaire by a patient. The Rose questionnaire,[16] developed in 1962, was the first PAD symptom questionnaire. It attempted to standardize the one and only symptom thought to be indicative of PAD at the time, claudication. Originally, the Rose questionnaire was developed for use in epidemiologic studies to determine prevalence rates and it was subsequently adopted by the World Health Organization (WHO) in 1968.[25] In 1977, minor changes were made to the wording of the questionnaire to make it suitable for self-administration; claudication criteria remained unchanged.[26] Results of the initial study revealed 91.9% sensitivity and 100% specificity in 37 patients with undoubted claudication (most verified by arteriograms) and 18 patients with other types of leg pain on walking (mainly sciatica, osteoarthritis, and calf cramps).[16] The WHO/Rose questionnaire failed to identify three participants with undoubted claudication, but correctly ruled out all of the participants reporting leg pain unrelated to claudication. Later studies with larger sample sizes, using physician diagnosis as a comparison (usually based on an ABI), resulted in a sensitivity and specificity as low as 8.6%[27] and 91%,[17] respectively. The low sensitivity in later studies may be explained by failure of the WHO/Rose questionnaire to identify participants reporting symptoms in an atypical location (e.g. buttock) or reporting symptoms in multiple locations, as having claudication. Further, a lower specificity may be explained when participants surveyed present with other types of non-ischemic leg pain and are classified as having claudication.

The low sensitivity and reduced specificity of the WHO/Rose questionnaire led to the development of the Edinburgh claudication questionnaire (ECQ) in 1992.[17] The revised questionnaire included a response for non-ambulatory patients and a lower extremity body diagram for patients to indicate leg symptoms in multiple locations. The body diagram allowed for claudication to be classified as definite claudication or atypical claudication depending on involvement (or lack thereof) of the calf. Initial testing of the ECQ revealed 91.3% sensitivity and 99.3% specificity in comparison to the diagnosis of claudication made by a physician.[17] The study population consisted of 50 new patients attending a peripheral vascular clinic with leg pain, aged over 55 years and 300 patients aged over 55 years visiting their general practitioner with any complaint.[17]

A new questionnaire, the San Diego claudication questionnaire (SDCQ),[18] was developed in 1996. The SDCQ was a revised and expanded version of the WHO/Rose questionnaire. It included buttock and thigh pain, which was also a component of the ECQ, but unlike the ECQ, the SDCQ inquired specifically whether symptoms were present in the right, left, or both legs. Of all the articles included in the review, the SDCQ was the most frequently used claudication questionnaire. Interestingly, all of the studies that utilized the SDCQ were conducted in the United States, whereas studies conducted abroad used the WHO/Rose and the ECQ.

Claudication questionnaires have undergone several revisions over time, but sensitivity remains low and specificity is variable. All three questionnaires are seemingly insensitive to

PAD detection compared to ABI as a gold standard for diagnosis. This indicates the need for further questionnaire refinement to increase the sensitivity and correctly identify patients with disease, but with symptoms differing in location and/or quality compared to those exhibiting classic claudication.

Symptom Definitions

A relatively strict definition of claudication (the 'typical' PAD symptom) has persisted over time. As previously described, in its original form,[16] classic claudication, is exertional pain restricted to one or both calves that causes a patient to slow down or stop walking, resolves within 10 minutes of standing still, does not resolve while the patient is walking, and does not begin at rest. While the introduction of the ECQ allowed for the presence of symptoms elsewhere in the lower extremities, pain still had to be present in one or both calves to be classified as definite claudication.[17,28,29]

The creation of the SDCQ allowed for the presence of more specific symptom categories beyond classic claudication, and the assessment of leg-specific symptoms (right versus left).[18] The SDCQ consists of five possible symptom categories per leg: Rose claudication, non-Rose exercise calf pain, previously referred to as 'possible IC'[28] and 'probable IC,'[29] non-calf exercise leg pain, pain at rest, and no pain.[18] Table 2 summarizes the evolution of claudication questionnaires, including symptom categories and their associated characteristics that most frequently appear in the literature.

Despite the evolution of these questionnaires, patients reporting pain in the hamstrings, feet, shins, joints, or radiating pain in the absence of calf pain would still not classify as 'symptomatic,' and subsequently would not be suspected of having PAD. Furthermore, although the number of symptom categories has increased on questionnaires, none allow for the reporting of symptom descriptors such as tingling, numbness, burning, throbbing, or shooting that have been reported by patients with PAD as being part of the symptom experience.[23,24]

Symptom Report

Typical Symptoms

The symptom most frequently recognized as the hallmark sign of arterial insufficiency is claudication. Claudication comes from the Latin word *claudicare*, meaning to limp. But, the use of this term is misleading, as patients who experience symptoms other than classic claudication are still shown to be functionally limited[30,31] and report a decreased quality of life.[32] Aside from confusion about the meaning of claudication, using classic claudication as the gold standard for PAD symptom recognition results in significant under-diagnosis of disease. Over the last ten to fifteen years, the reported prevalence of classic claudication in patients with symptomatic PAD has been highly variable, ranging from 7.5%[20] to 33%.[18,21,22] Higher prevalence has been reported in smaller populations (43.8%)[33] and specific populations including only individuals complaining of leg pain (78.8%),[34] or excluding individuals who have non-compressible arteries, CLI, or a history of revascularization (43.6%).[35] Overall, study results indicate that there are specific characteristics of individuals who are more likely to report classic claudication. Reporting appears to increase as age increases,[21,28,29,36,37] and be more prevalent among men,[21,36,37] and in individuals with diabetes,[21] hypertension,[38] a previous diagnosis of PAD,[2,18] or a more severe form of the disease.[18,21,37] Disease location may also influence the reporting of classic claudication, with higher prevalence among those with distal lesions[35] or large vessel PAD.[28]

The highest reported prevalence of classic claudication is 100%.[39–41] The most recent study conducted by Gardner and colleagues[40] included 114 participants with symptomatic PAD recruited from vascular and primary care clinic referrals. Prior to exercise testing, participants fell into the following three symptom categories: leg pain on exertion and rest (40.3%), atypical leg pain (27.2%), and classic claudication (32.5%). However, during a graded treadmill test, all of the participants reported symptoms consistent with classic claudication. In 2007, Gardner and colleagues[39] reported similar findings. The study included 715 participants self-reporting exertional leg pain consistent with one of the first four categories on the SDCQ. Initial classic claudication prevalence was 56.8%. As with the 2012 study, during treadmill testing, all of the study participants experienced exertional leg pain that was consistent with classic claudication (i.e. participants stopped walking due to calf pain that resolved with subsequent rest). McDermott and colleagues[41] reported similar findings with a group of 57 patients who initially self-reported no symptoms, but over half became symptomatic during a 6-minute walking test. These results raise important questions that have not been previously explored: *Are the patients classified in the literature as 'asymptomatic' truly not experiencing symptoms, or are they slowing their walking pace or limiting ambulation to prevent the onset and/or progression of leg symptoms which could be revealed under controlled exercise testing?* The issue of under-reporting versus true symptom prevalence deserves further attention.

Atypical Symptoms

When Rose[16] developed the first claudication questionnaire in 1962, the characteristics of PAD were thought to be well-delineated, which made it suitable for diagnosis in epidemiologic surveys. However, over the last five decades, researchers have discovered a more diverse presentation of PAD symptoms. With classic claudication consistently being reported by less than one-third of patients with PAD, claudication questionnaires have been forced to evolve in order to capture the broad array of symptom experiences.[17,18] But, revised claudication questionnaires are still not sufficient, as patients are reporting symptoms and symptom experiences that are not detected by these questionnaires. Until a more comprehensive tool exists, it is essential for clinicians to recognize that patients with underlying PAD are reporting 'atypical' symptoms more frequently than classic claudication,[2,20,22,27,42–45] and adapt their assessment techniques accordingly.

In the literature reviewed, the prevalence of atypical symptoms was difficult to ascertain compared to classic claudication, despite its increased frequency. The main reasons were the use of a variety of definitions for atypical symptoms and inconsistent use of symptom categories from study to study. In its simplest form, atypical symptoms included any lower extremity symptom that was not consistent with classic claudication[2,18] and increased in complexity to include all lower extremity symptoms not located in the calf,[17] exercise calf pain not present at rest, but otherwise not fully concordant with the Rose criteria ('possible IC'),[28,46] calf pain, but one Rose criteria not fulfilled ('probable IC'),[29] atypical pain on exertion (non-Rose walk-through pain and non-Rose stop because of pain), and pain on exertion and rest.[39,41] Atypical pain was used to refer to 'walk-through pain' and/or pain that was not consistently relieved within 10 minutes of rest.[38] However, prolonged symptom recovery was also grouped together with pain at rest into a 'no pain' category.[47] Pain that presented at rest and on exertion was often referred to as 'leg pain on exertion and rest,'[21,39–41,45] but was also referred to as 'pain at rest,'[18,22,42,48] 'rest pain,'[43,49] or 'symptoms at rest.'[35] Some studies subdivided the 'no symptoms with exertion' category into active and inactive participants, resulting in a total of six leg categories,[41,50] whereas Collins and colleagues[20] condensed the five symptom categories of the SDCQ into three: no pain, atypical leg pain, (pain at rest, non-calf exercise pain, and non-Rose exercise calf pain) and Rose claudication. Others followed the original five symptom categories established by

the SDCQ[21] or used a general category of 'leg symptoms'[44] or 'symptomatic' that included lower extremity revascularization, amputation secondary to PAD, or report of claudication regardless of ABI.[51] The use of either category, 'leg symptoms' or 'symptomatic,' limits the understanding of symptom presentation by classifying symptomatic patients as asymptomatic and vice versa.

Discovering a wider variety of PAD symptoms has not been entirely without challenge, particularly since responses to some symptom categories can be difficult to interpret. For example, the rest pain category on the SDCQ could represent an individual experiencing ischemic rest pain or pain at rest not associated with PAD, but attributable to a comorbid condition such as arthritis. Additionally, it is imperative that symptoms consistent with ischemia are differentiated from those not consistent with ischemia in order to identify atypical PAD symptoms versus manifestations of comorbid conditions unrelated to PAD (i.e. symptom confounders). Figure 2 illustrates how a symptom can be classified as ischemic or non-ischemic in three phases: at rest, during exercise, and during recovery.

Potential Symptom Confounders

It has been demonstrated that older adults are more likely to become afflicted with PAD.[52,53] Older age also makes it more likely that patients with PAD are afflicted with other age-related conditions that could cause or contribute to lower extremity symptoms. Consideration should also be given to PAD severity and its influence on the symptom experience. While several researchers have recognized the potential influence of comorbid conditions on symptom presentation,[24,27,41,42,53–56] the topic has not been thoroughly researched or reported in the literature. Findings from McDermott and colleagues[41] revealed an increased prevalence of diabetes, neuropathy, and spinal stenosis in patients who reported pain on exertion and rest. Similarly, Newman and colleagues[27] discovered a higher prevalence of arthritis and depression in patients reporting exertional leg pain other than classic claudication. Findings from Bernstein and colleagues[57] revealed a low prevalence of classic claudication (2%) among patients with PAD, half of whom were also diagnosed with degenerative joint disease. Insulin resistance without a diagnosis of diabetes has also been identified as a factor influencing claudication prevalence.[58] Further support for the effect of comorbid conditions came from a study conducted by Weinberg and colleagues,[54] indicating that regional neuropathy is commonly associated with chronic ischemia and CLI.

The neuropathic component of ischemic pain has been examined more closely by researchers and the current understanding is that the character of ischemic pain changes from nociceptive pain in patients with classic claudication to predominately neuropathic pain in patients with CLI.[24] Despite the large numbers of patients diagnosed with PAD and reporting neuropathy, the knowledge of the role of ischemia in neuropathic pain remains limited. Overall, these preliminary results suggest that there are differences in the symptoms reported and/or differences in the character of the symptom in the presence of certain comorbid conditions or in those with severe PAD (i.e. CLI). This provides additional evidence that using classic claudication as the defining symptom of PAD is insufficient to capture the breadth of symptoms experienced, particularly in this patient population.

Similarly, differential diagnoses have been described in PAD literature in an attempt to clear the blurring of symptom reporting that occurs in the presence of multiple comorbidities, but it has not been extensively studied.[59–65] An understanding of physiology can allow a clinician to locate the site of arterial occlusion based on the location of the symptom(s). For example, pain or discomfort in the calf, ankle, or foot could indicate an obstruction/occlusion in the popliteal or superficial femoral arteries.[60] Symptoms located primarily in the calf or thigh could indicate involvement of the femoral arteries or their branches,

whereas, symptoms in the buttock, hip, and thigh indicate higher disease in the aorta or iliac artery.

The location of symptoms can serve as a guide, but they do not guarantee the presence or location of a lesion with 100% certainty. Symptoms of a patient with claudication may overlap with symptomatology of other conditions, particularly neurological and musculoskeletal diseases.[63] Take for instance a patient reporting calf pain. The pain could indicate claudication secondary to a femoral artery occlusion or it could indicate a venous occlusion, chronic compartment syndrome, nerve root compression, or a Baker's cyst (a tight bursting pain/dull ache that worsens on standing and resolves with leg elevation).[59,61,63,66] The presence of any of these conditions could lead a provider to suspect claudication, which could be ruled out if the symptom is relieved by a change in position. Symptoms in the hip, thigh, or buttock could be related to hip arthritis.[59,63] However, arthritis is usually a more persistent pain compared to the intermittent nature of claudication and typically associated with symptoms in other joints.[63,67] Spinal cord compression should also be considered, particularly when a patient is reporting a history of back pain, with symptoms that worsen upon standing, but are relieved by positional changes.[59] Patients reporting foot symptoms could have an inflammatory condition such as arthritis or Buerger's disease.[63,64] Current clinician recommendations are to conduct a thorough physical exam and symptom assessment that includes the location, duration, and intensity.[62] If PAD is suspected based on patient symptom report or a patient's risk factor profile, a confirmatory ABI should be performed.

Conclusions and Recommendations

Claudication questionnaires have been used extensively to assess the presence of claudication and subsequently to detect the presence of PAD. Although often highly specific, they remain insensitive for the detection and diagnosis of PAD. Additionally, the inconsistent use of one standardized questionnaire, combined with variations in sample characteristics, definition of PAD, diagnostic methods, and definition of claudication and atypical symptoms make comparisons across studies difficult, if not impossible. Although appearing more frequently, the non-specific nature of atypical symptoms further complicates clear symptom categorization and necessitates classification of atypical symptoms as being caused by ischemia or caused by comorbid conditions unrelated to ischemia. Furthermore, age and gender differences may affect the reporting of classic claudication and atypical symptoms on PAD questionnaires. However, the largest confounder of PAD symptom report may be the presence of comorbidities, particularly those that affect mobility, as physical limitations may preclude manifestation of PAD symptoms and delay necessary diagnosis and treatment. As the role of comorbid conditions becomes more clearly defined, follow up questions can be added to existing questionnaires to eliminate false positives and to capture participants who were originally considered false negatives.

Additional research is needed to increase understanding of the role of age, gender, race, and comorbid conditions on the symptom experience of patients with PAD. The next logical step is to validate subjective symptom report with objective physiologic measures that detect ischemia during exercise in an attempt to broaden the current understanding of PAD symptom presentation. Better understanding and differentiation of symptoms that are not consistent with classic claudication or atypical symptoms caused by ischemia, but rather caused by a comorbid condition that is unrelated to ischemia, is essential to enhance understanding of the symptom experience. While previous research has correlated symptom report with PAD disease severity as measured by ABI, to the authors knowledge, they have been conducted in a static state. Simultaneous data collection during dynamic exercise has the potential to provide new symptom descriptors that are necessary to consistently and

accurately detect PAD based on patient characteristics and vague symptom reporting, thus expanding the definition of 'claudication.' These additional descriptors could be incorporated into existing PAD questionnaires, thus enhancing the sensitivity of these questionnaires, potentially leading to improved detection and treatment of PAD.

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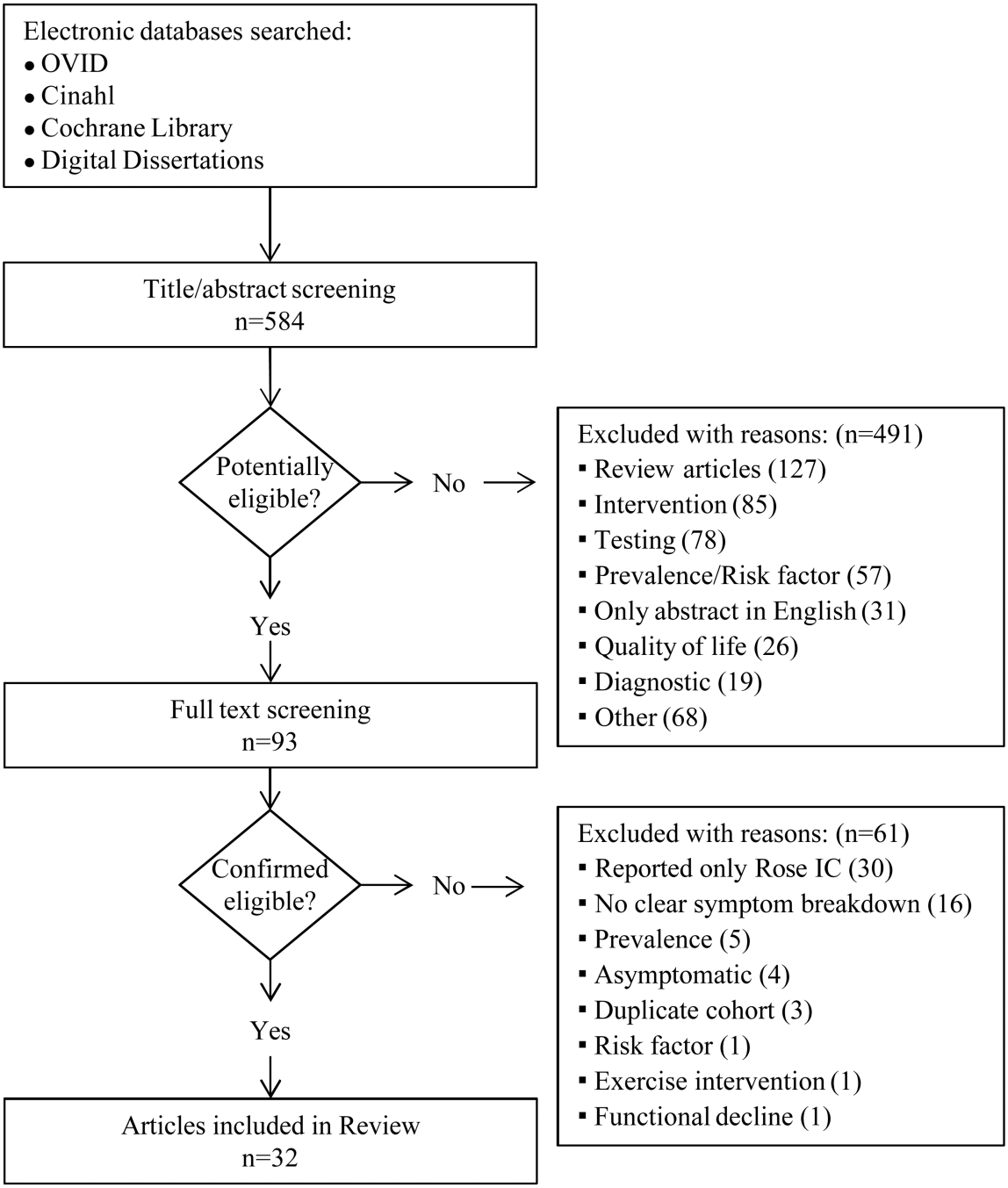

Figure 1.
Structured Literature Review Search Process

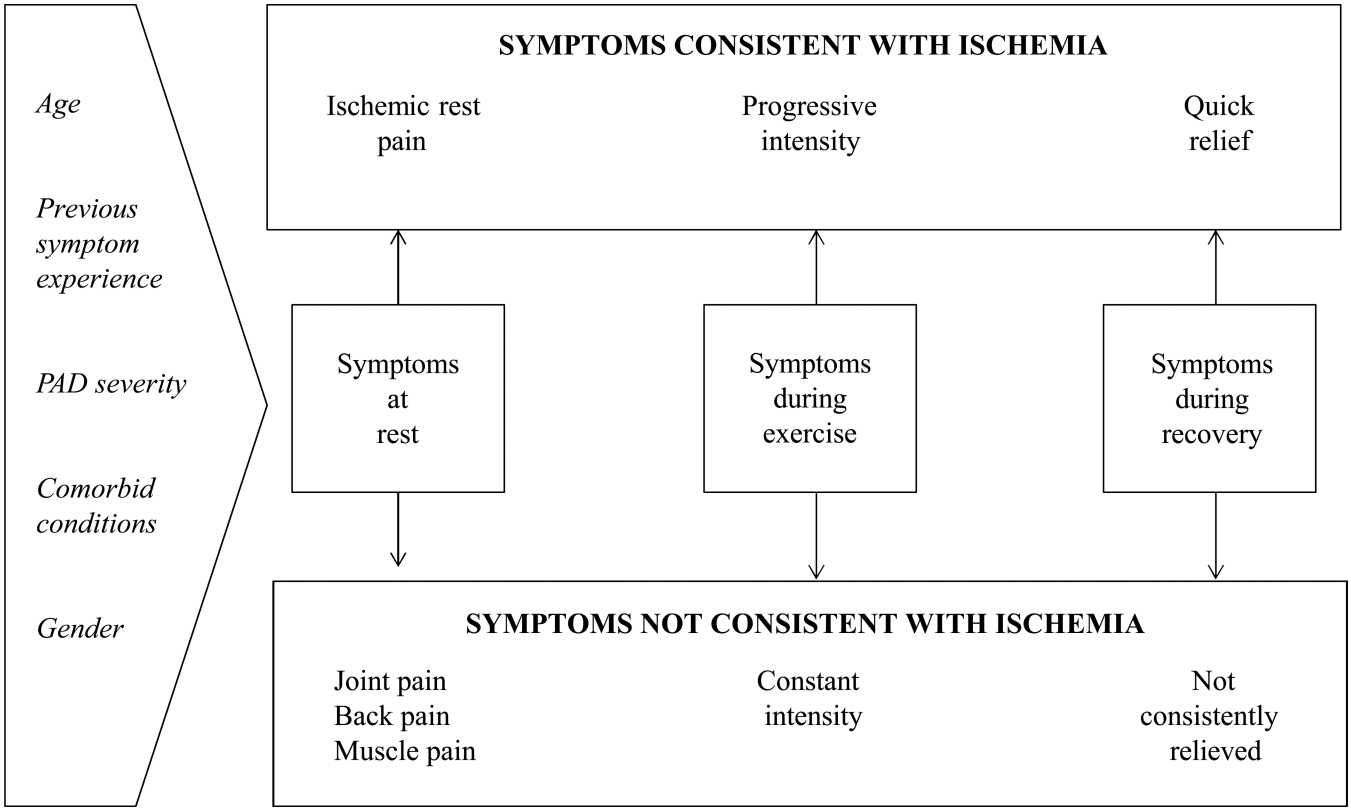

Figure 2.
Conceptual Model of Symptom Differentiation

Table 1

Results of the structured review.

First author	Population characteristics: Sample size	Mean age (Range)	Male (%)	Mean ABI	Selection criteria	Symptom tool	Symptom(s): Sensitivity	Specificity (Gold standard)	Symptom prevalence: Entire sample	PAD sample
Rose[16]	55	54.2	85%	—	Hospitalized patients with ischemic heart disease A = Undoubted IC B = Other types of exertional leg pain	Rose*	Rose IC		Rose IC	
	A=37	57.1	86%	—			91.9%	100%	61.8%	91.9%
	B=18	48.2	83%	—			(Physician diagnosis)			
Criqui[28]	613	66 (38-82)	45%	—	Original cohort; free-living population with elevated cholesterol, triglycerides, or on lipid lowering medication[68,69]	WHO/Rose[25]	Possible IC		No pain	
							4.5%	96.9%	94.1%	80%
							Rose IC		Possible IC	
							9.2%	99%	4%	10.8%
							Possible IC + Rose IC		Rose IC	
							20%	95.9%	1.9%	9.2%
							(Non-invasive diagnostic testing; large vessel PAD only)		(Large vessel PAD only)	
Fowkes[29]	1592	— (55-74)	51%	1.03	Age-stratified random sampling from 10 general medicine practices	WHO/Rose	Probable IC + Rose IC		No pain	
							14.9%	97.8%	95.4%	—
							(ABI[§])		Probable IC	
									1.1%	—
									Rose IC	
									3.5%	—
Leng[17]	A=586	67.9	—	—	A = Known claudicants participating in a follow up study B = Exertional leg pain due to other causes identified from a diagnostic register C = Community patients attending their GP with any complaint D = Clinic patients with leg pain	WHO/Rose (A&B) ECQ (C&D)	Rose IC (A&B)		ECQ IC (C)	
							60%	91%	7.4%	91.3%
	B=61	62.6	—	—			Possible IC + Rose IC (A&B)		Possible IC (D)	
							91%	72%	8%	—
	C=300	70.2	—	—			ECQ IC (C)		Atypical IC (D)	
							91.3%	99.3%	4%	—
	D=50	62.4	—	—			ECQ IC (D)		ECQ IC (D)	
							82.8%	100%	58%	82.8%
							(Physician diagnosis & non-invasive diagnostic testing)			
Criqui[18]	508 (980 legs)	68 (39-95)	88%	—	VA and University hospital vascular laboratory patients (surviving 6 months to 14 years	SDCQ	Pain at rest		No pain	
							23.4%	71.9%	31.1%	24%
							Non-calf exercise pain		Pain at rest	

					after their initial visit)		4% 96.5% Non-Rose exercise calf pain (walk-through) 15.1% 89% Rose IC 33.4% 89% Any symptom category 76% 46.5% (ABI, Peak PT, & TBI)	24.9% 23.4% Non-calf exercise pain 3.9% 4% Non-Rose exercise calf pain (walk-through) 13.8% 15.1% Rose IC 26.3% 33.4%
Leng[36]	A=1592 B=1498	— (55-74) — (60-80)	51% 52%	1.03 —	A = Original cohort selected randomly from 10 general practices[29] B = Original participants available for 5-year follow-up study	WHO/Rose (n=1287)	— (UTC)	Probable IC (B) 3.8% — Rose IC (B) 3.3% —
Stoffers[37]	A=18884 B=3171 C=417 D=886	58.6 (45-74) 59.8 (45-74) 60 58	47% 47% 69% 40%	— — — —	A = Base population (segment of the general population) B = Stratified sample of the general population (spectrum of vascular & cardiovascular risk) C = PAD known to GP D = PAD unknown to GP	WHO/Rose	Any symptom category (B) 22% 94.5% (ABI <0.95)	Non-Rose IC (B) 3.7% — Only non-calf IC (B) 1.2% — Rose IC (B) 1.6% — Any symptom category (B) 6.6% —
McDermott[70]	268 A=137 B=26 C=105	70.1† 71.9 69 68	50%† 58% 31% 45%	0.77† 0.55 0.71 1.06	A = PAD patients identified from blood flow laboratory B = PAD patients from general internal medicine practice via ABI C = Non-PAD from general internal medicine practice via ABI	SDCQ	Pain at rest 31.3% 85.7% Atypical IC 22.7% 95.2% Rose IC 24.5% 96.2% Any symptom category 78.5% 77.1% (ABI <0.9)	No exertional leg pain 43.3% 21.5% Pain at rest 24.6% 31.3% Atypical IC 15.7% 22.7% Rose IC 16.4% 24.5%
McDermott[22]	214 A=147 B=67	70.4† 71.5 68	55%† 55% 54%	0.72† 0.56 1.06	A = PAD patients from non-invasive vascular laboratory and vascular surgery B = Control patients from general internal medicine	SDCQ	Pain at rest 29.9% 88.1% Non-Rose IC 25.2% 92.5% Rose IC	No exertional leg pain 34.6% 15.6% Pain at rest 24.3% 29.9% Non-Rose IC

						29.3% 95.5% Any symptom category 84.4% 76.1% (ABI <0.9)	19.6% 25.2% Rose IC 21.5% 29.3%
Hirsch[2]	6417	70. 3†	47%†	1.00†	Primary care clinic patients stratified by age and risk factor profile	SDCQ	Atypical IC 55.5% 57.3% Rose IC 10.6% 97.8% Atypical IC + Rose IC 66% 55.1% (ABI)	No pain 47.9% 34% Atypical IC 47.1% 55.5% Rose IC 5% 10.6%
Matzke[15]	100 A=63 B=37	71 (38-95) 71 (43-95) 72 (38-94)	60% 65% 51%	— — —	Symptomatic CLI recruited from a vascular outpatient clinic A = Claudication symptoms prior to CLI B = CLI as the initial symptom of PAD	SDCQ and additional questions regarding occurrence of rest pain, ulcers, or gangrene	Claudication 63% UTC (European Consensus Document criteria for ischemia[71])	No Claudication — 37% Claudication — 63%
McDermott[41]	590 A=460 B=130	70.9 71.8† —	56% 59%† —	— 0.65† —	A = PAD diagnosed in non-invasive vascular laboratories B = Non-PAD patients identified from GP	SDCQ	Pain at rest 19.1% UTC Atypical IC (carry-on) 8.9% UTC Atypical IC (stop) 19.6% UTC Rose IC 32.6% UTC Any symptom category 80.2% UTC (ABI <0.9)	No exertional leg pain — 19.8% Pain at rest — 19.1% Atypical IC (carry-on) — 8.9% Atypical IC (stop) — 19.6% Rose IC — 32.6%
Newman[27]	5572 A=4358 B=1124 C=90	— 72.7 73 74.9	42% 44% 38% 51%	— — — —	Random sample of Medicare enrollees A = No exertional leg pain B = Exertional leg pain (non-Rose) C = Rose IC	WHO/Rose	Non-Rose IC 32.4% 81.6% Rose IC 8.6% 99.4% Rose IC + Exertional leg pain 40.9% 81.1% (ABI <0.9)	No exertional leg pain 78.2% 59% Non-Rose IC 20.2% 32.4% Rose IC 1.6% 8.6%

Collins[20]	403 A=67 B=336	63.8 65.3 63.5	48% 51% 48%	1.06† 0.72 1.13	Patients visiting primary care clinician at VA Medical Center or primary care clinic A = PAD B = No PAD	SDCQ	Atypical IC 55.2% 50.9% Rose IC 7.5% 98.5% Atypical IC + Rose IC 62.7% 49.4% (ABI <0.9)	Atypical IC 50.1% 55.2% Rose IC 2.5% 7.5%
Ogren[38]	A=703 B=389 C=88	55 68 68	100% 100% 100%	— 1.00† —	A = Original cohort[72] B = Original participants living and willing to participate in a follow-up study[18] C = Eligible participants not included in the original cohort	WHO/Rose (n(A)=700)	Atypical IC (A) 14.3% 79.1% Rose IC (A) 71.4% 97.7% Atypical IC + Rose IC (A) 85.7% 76.8% Atypical IC + Rose IC (B) 14.9% 98% (Calf plethysmography (A); ABI <0.9 (B))	No leg pain (A) 76.1% 14.3% Atypical IC (A) 20.9% 14.3% Rose IC (A) 3% 71.4% No leg pain (B) 96.2% 85.1% Atypical IC + Rose IC (B) 3.8% 14.9%
Wang[21]	3629 (7278 legs) A=508 (1001 legs) B=740 (1479 legs) C=2401 (4798 legs)	62.9 68.6 70.9 59.3	46% 88% 56% 34%	— — — —	Cross-sectional analysis of three cohort studies A = Recruited from vascular laboratories[73] B = Recruited from non-invasive vascular laboratories and general medical practice[41] C = Free living population randomly selected via computer database[74]	SDCQ	Pain at rest 18.2% 83.7% Non-calf IC 4.2% 98.9% Atypical IC 16% 96.8% Rose IC 31.4% 97.8% Any symptom category 69.9% 81.8% (ABI and/or history of revascularization)	No Pain 71.4% 30.1% Pain at rest 13% 18.2% Non-calf IC 1.7% 4.2% Atypical IC 5.8% 16% Rose IC 8.1% 31.4%
Gardner[39]	715 A=103 B=125 C=81 D=406	68† 67 69 68 68	80%† 78% 82% 86% 79%	0.69† 0.71 0.68 0.69 0.68	Free living population with exercise limiting leg pain and an ABI <0.9 recruited from a vascular clinic and advertisements A = Leg pain on exertion and rest B = Atypical exertional pain (stop) C = Atypical exertional pain	SDCQ	Pain at rest 14.4% NA Atypical exertional (carry-on) 11.3% NA Atypical exertional (stop) 17.5% ** Rose IC	Pain at rest 14.4% ** Atypical exertional (carry-on) 11.3% ** Atypical exertional (stop) 17.5% ** Rose IC

					(carry on) D = Rose IC		56.8% | ** (ABI <0.9) ** 100%; all symptomatic PAD patients	56.8% | ** **100% reported Rose IC during treadmill test
Makdisse[34]	217 A=52 B=162	60 (30-86) 65.8 58.2	46% 62% 41%	— — —	Individuals with complaints of leg pain recruited through mass communication media A = PAD B = No PAD	ECQ (Brazilian Portuguese version)	Atypical IC (non-calf) 5.8% | 99.4% Rose IC 78.8% | 93.9% Atypical IC + Rose IC 84.6% | 93.3% (ABI)	Atypical (non-calf) 1.8% | 5.8% Rose IC 23.5% | 78.8%
Missault[51]	2831 A=1777 B=1054	68 69 66.2	70% 70% 70%	0.90 0.80 1.00	High-risk (CAD and/or CVD) ambulatory patients referred by their physician A = PAD B = No PAD	ECQ	ECQ IC (Definite + Atypical) 52.4% | 82.7% (ABI <0.9 and/or history of revascularization)	Walking pain 45.7% | 66.7% Uphill/hurrying 42.5% | 64.4% Ordinary pace 25% | 36.6% Standing/Sitting 6.4% | 5.6%
Sprynger[46]	4536 A=842 B=3649 *ABI missing for 45 patients	67 (18-98) — —	60% — —	1.02* — —	Asymptomatic high-risk patients referred by GP (previous ischemic attack or PAD risk factors) A = PAD B = No PAD	ECQ (n=842)	Expanded Rose IC (legs/calves) 45.6% | UTC (ABI <0.9)	Uphill/hurrying * | 56.7% Carry on at same speed * | 3.7% Slow down * | 18.2% Stop * | 34.8% Expanded Rose IC (legs/calves) * | 45.6% *Only those with PAD completed ECQ
Bernstein[57]	50	63 (50-86)	100%	—	Patients presenting to orthopedic surgical practice for evaluation of non-traumatic lower extremity pain with no history of PAD	Telephone interview: 1. Leg pain? 2. Pain on exertion: • With every	Claudication 10% | 100% (ABI <0.9 and/or abnormal PVR's)	Claudication 2% | 10%

						bout of activity • Increases with activity • Improves with rest		
Lacroix[43]	291 A=21 B=34 C=31 D=205	69.5 (43-97) 69.2 72.1 76.8 68.8	53% 71% 59% 65% 48%	— — 0.71 — —	Patients hospitalized in a tertiary care center for non-PAD related disorders (excluded vascular department) A = History of PAD B = Unrecognized PAD (ABI ≤0.9) C = Unrecognized PAD (ABI ≥1.4) D = No PAD	ECQ (French version)	Pain at rest 16.3% 84.9% Walking pain 29.1% 82% Rose IC 12.8% 97.1% (ABI)	Pain at rest (‘rest pain’) 15.5% 16.3% Walking Pain 24.4% 29.1% Rose IC 5.8% 12.8%
Ruger[24]	102 A=61 B=41	68.1 68.1 68	62% 69% 51%	0.58 0.70 0.40	Inpatients at angiology and vascular surgery center with PAD and chronic ischemic pain (excluded neuropathy of other origin) A = CI B = CLI	SF-MPQ (assesses pain quality)	NA	IC pain descriptors (*rated as most severe*): *stabbing, cramping, aching, and tiring-exhausting* CLI pain descriptors (*rated as most severe*): *throbbing, *shooting, **stabbing, **hot-burning, **tender, tiring-exhausting, and **punishing-cruel* *statistically significant difference in the ratings between groups
Kownator[44]	5679 A=1340 B=357	69.1 70.9 —	63% 71% 74%	— — —	Original cohort; free living population at high-risk for PAD visiting GP[75] A = Subset of original cohort with isolated CAD, but without cerebrovascular disease or a known history of PAD B = PAD identified in subset	Physician physical exam, questioning (details not reported), and medical record	IC only (A) 20.4% 94.3% Any leg symptom (A) 49% 76.6% (ABI <0.9)	Leg symptoms (includes IC) 34.8% — IC 15.2% — Leg symptoms (A) 30.2% 49% IC (A) 9.6% 20.4%
Manzano[47]	1487 A=122	66.2 68.3	58% 64%	— —	Patients referred to internal medicine service with vascular risk but no known atherosclerotic	ECQ (modified algorithmic	Atypical IC (non-calf) 13.2% 96.9% Rose IC	No pain 87% 69% Atypical IC

	B=27	68.8	57%	—	disease A = PAD and IC B = PAD and no symptoms	method)	17.8% 96.5% Atypical IC + Rose IC 31% 93.4% (ABI <0.9)	5.8% 13.2% Rose IC 7.2% 17.8%
Mourad[48]	2146	72.4	52%	0.92	Hospitalized patients with high cardiovascular risk, not previously diagnosed with PAD	Physician assessment (details not reported)	UTC (symptom categories not clearly defined)	Pain in lower limb 20.5% — Pain at rest 9.8% — Non-IC 11.9% — IC 4.3% —
Tomczyk[23]	A=38 B=20	65 (44-83) 63.4 (44-83)	63% 50%	— —	A = Entire cohort; recruited from two medical centers, symptomatic PAD[32] B = Convenience sample; severity ranged from claudication to ischemic pain and non-healing wounds	Interactive interviews (content analysis)	NA	Characteristics of symptom descriptions theme (B): *I. Somatic Descriptions: cramping; aching; pain; hurt; sore; tired* II. Non-Sensational Expressions *III. Atypical or Comorbid Symptoms: tingling; no feeling; numbness; cold and hot; sores* IV. Euphemisms
Siddiqi[49]	350	53 (30-80)	71%	1.03	Patients presenting with acute coronary syndrome at a tertiary care center	Interview and physical exam	Ischemic Rest Pain 33.9% 94.1% Claudication 48.4% 71.5% Ischemic Rest Pain + Claudication 67.7% 67% (ABI <0.9)	Pain at rest (‘rest pain’) 10.9% 33.9% Claudication 32% 48.4%
Makowsky[33]	361 A=16 B=345	65.1 70.1 64.9†	45% 50% 44%†	1.13† 0.79 1.15†	At-risk population visiting ambulatory health settings A = PAD B = No PAD	ECQ	Atypical IC 12.5% 99.1% Rose IC 43.8% 96.8% Atypical IC + Rose IC	No Claudication 93.6% 43.8% Atypical IC 1.4% 12.5% Rose IC

							56.3% 95.9% (ABI)		5% 43.8%
McDermott[45]	427 A=393 B=34	69.7 69.4 72.1	66% 69% 32%	0.70 0.67 1.12	A = Low-risk, non-PAD recruited from general internal medicine practice B = PAD patients recruited from non-invasive vascular laboratories	SDCQ	Pain at rest 26.2% 82.4% Atypical IC, carry-on 10.4% 97.1% Atypical IC, stop 19.3% 88.2% Rose IC 24.4% 100% Any symptom category 80.4% 67.6% (ABI <1.00)		No Pain 23.4% 19.6% Pain at rest 25.5% 26.2% Atypical IC, carry-on 9.8% 10.4% Atypical IC, stop 18.7% 19.3% Rose IC 22.5% 24.4%
Gardner[40]	114 A=46 B=31 C=37	64.1† 62 66 65	54%† 48% 55% 60%	0.72† 0.81 0.69 0.63	Patients with symptomatic PAD recruited from vascular and primary care clinic referrals and newspaper advertisements A = Pain at rest B = Atypical IC C = Rose IC	SDCQ	Pain at rest 40.3% — Atypical IC 27.2% — Rose IC 32.5% — (ABI ≤ 0.9 or ABI ≤0.73 after exercise)		Pain at rest 40.3% ** Atypical IC 27.2% ** Rose IC 32.5% ** **100% reported Rose IC on graded TM test
Zitteren[35]	701	64.8 (37-92)	64%	—	Newly diagnosed, symptomatic PAD recruited from two vascular surgery outpatient clinics	SDCQ (n=622)	Pain at rest 21.4% — Atypical IC 31.2% — Rose IC 43.6% — Any symptom category 96.1% — (ABI ≤ 0.9 or 15% drop in ABI after exercise)		No pain 3.9% NA Pain at rest 21.4% NA Atypical IC 31.2% NA Rose IC 43.6% NA

ABI=ankle-brachial index; PAD=peripheral artery disease; — =not reported; IC=intermittent claudication; *Rose questionnaire adopted by the World Health Organization (WHO) in 1968 for use in epidemiological surveys; §PAD diagnostic criteria was ABI ≤ 0.9 unless indicated otherwise[76]; GP=General Practitioner; ECQ=Edinburgh Claudication Questionnaire; VA=Veterans Affairs; SDCQ=San Diego Claudication Questionnaire; Peak PT=peak velocity in the posterior tibial artery; TBI=toe-brachial index; UTC=unable to calculate; †=calculated; CLI=critical limb ischemia; CAD=coronary artery disease; CVD=cerebrovascular disease; PVR=pulse volume recordings; CI=chronic ischemia; SF-MPQ=Short-Form McGill Pain Questionnaire; NA=not applicable

Table 2

Evolution of claudication questionnaires.

Questionnaire	Year created/ revised	Symptom category	Symptom characteristics

Rose[16] WHO/Rose[25]	1962	• Intermittent Claudication (Rose IC)
		  ■ Grade 1
		  ■ Grade 2
			• Exertional calf pain
			  ■ Walking uphill or hurrying
			  ■ Walking at ordinary pace on the level
			• Never starts at rest (standing/sitting)
			• Never disappears while walking
			• Causes patient to slow down or stop
			• Usually disappears in 10 minutes or less

	1985	• Possible IC[28]	• Exertional calf pain • Never starts at rest • Otherwise not fully concordant with the Rose IC criteria
	1991	• Probable IC[29]	• Exertional calf pain • One WHO/Rose criteria not fulfilled

ECQ[17]	1992	• Definite IC (Rose IC)
		  ■ Grade 1
		  ■ Grade 2
		• Atypical IC
			• Fully concordant with Rose IC criteria
			  ■ Walking uphill or hurrying
			  ■ Walking at ordinary pace on the level
			• Pain in thigh or buttock in the absence of calf pain, otherwise concordant with Rose IC criteria

SDCQ[18]	1996	• Rose IC • Non-Rose exercise calf pain • Non-calf exercise leg pain • Leg pain on exertion and at rest • No pain	• Fully concordant with Rose IC criteria • Exertional calf pain; at least one Rose IC criteria not fulfilled • Pain in either leg excluding calf (can be thigh or buttock), does not begin at rest • Exertional leg pain starts at rest • Reports no pain in calf, thigh, or buttock