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AHA SCIENTIFIC STATEMENT

State of the Science: The Relevance of Symptoms in Cardiovascular Disease and Research: A Scientific Statement From the American Heart Association

Corrine Y. Jurgens, PhD, RN, ANP, FAHA, Chair; Christopher S. Lee, PhD, RN, FAHA, Vice Chair; Dawn M. Aycock, PhD, RN, ANP-BC, FAHA; Ruth Masterson Creber, PhD, MSc, RN, FAHA; Quin E. Denfeld, PhD, RN, FAHA; Holli A. DeVon, PhD, RN, FAHA; Linda R. Evers, JD; Miyeon Jung, PhD, RN, FAHA; Gianluca Pucciarelli, PhD, RN, FAHA; Megan M. Streur, PhD, RN, FNP; Marvin A. Konstam, MD, FAHA; on behalf of the American Heart Association Council on Cardiovascular and Stroke Nursing; Council on Hypertension; and Stroke Council

ABSTRACT: Symptoms of cardiovascular disease drive health care use and are a major contributor to quality of life. Symptoms are of fundamental significance not only to the diagnosis of cardiovascular disease and appraisal of response to medical therapy but also directly to patients' daily lives. The primary purpose of this scientific statement is to present the state of the science and relevance of symptoms associated with cardiovascular disease. Symptoms as patient-reported outcomes are reviewed in terms of the genesis, manifestation, and similarities or differences between diagnoses. Specifically, symptoms associated with acute coronary syndrome, heart failure, valvular disorders, stroke, rhythm disorders, and peripheral vascular disease are reviewed. Secondary aims include (1) describing symptom measurement methods in research and application in clinical practice and (2) describing the importance of cardiovascular disease symptoms in terms of clinical events and other patient-reported outcomes as applicable.

Key Words: AHA Scientific Statements ■ arrhythmias ■ cardiovascular disease ■ coronary artery disease ■ heart failure ■ patient-reported outcomes ■ peripheral vascular disease ■ stroke

Symptoms are subjective experiences that may indicate disease or significant change in health status. Symptoms have been linked to cardiovascular disease (CVD) since Egyptian physicians and Hippocrates described fatigue and dyspnea, respectively, as being related to the failing heart.[1,2] In a contemporary view of CVD, symptoms often are critical elements of the diagnosis, evaluation, management, and certainly lived experience of illness. Symptoms also drive health care use and are a major contributor to broad patient-reported outcomes such as quality of life in chronic CVD.[3,4] More commonly, research in CVD is focused on major adverse cardiovascular events such as hospitalization or death in response to cardiovascular therapies and less so on symptoms despite their fundamental significance. The primary purpose of this scientific statement is to present the state of the science and relevance of symptoms associated with CVD. Symptoms as patient-reported outcomes are reviewed in terms of the genesis, manifestation, and similarities or differences between diagnoses. Secondary aims are to describe symptom measurement methods in research and to describe the importance of symptoms in terms of clinical events and other patient-reported outcomes as appropriate.

SYMPTOM TRAITS AND CAVEATS IN CVD

Although we frequently assume that symptoms are subjective experiences that accurately reflect underlying bodily changes, several caveats must be taken into consideration in the interpretation of symptoms in CVD (Table 1).

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Table 1. Symptom Definition, Characteristics, Traits, and Caveats

Definition	Subjective experiences that may indicate disease or change therein
Characteristics	Intensity, quality, duration, timing, distress, interference with life
Traits	Localized (for example, substernal chest pain) or generalized (for example, fatigue) experiences that can involve any of the body's senses[5]
Caveats	Bodily changes must be (1) different in intensity or frequency and (2) sufficient in magnitude, newness, or significance compared with normal bodily sensations to be detected as symptoms.[5,6]
	Bodily changes are interpreted as a function of their attribution (for example, fatigue from heart failure vs a normal aging process)[7,8] and within cultural norms.[9]
	Bodily changes may be misinterpreted (that is, symptoms can be experienced without underlying change in pathogenesis, or change in underlying pathogenesis may not be experienced as symptoms).
	External stressors may cause unawareness of major body changes or hypervigilance to even small changes in health.[10]
	Symptoms may be highly variable among patients with similar cardiovascular disorders.[10,11]
	Symptoms of CVD commonly occur in clusters.[12–14]

CVD indicates cardiovascular disease.

Most notably, patients with CVD may experience symptoms in the absence of major changes in underlying pathogenesis. The absence of symptoms also does not necessarily confer the absence of change in underlying pathogenesis, particularly in advanced CVD.[15] Nevertheless, symptoms have relevance in CVD, particularly in acute coronary syndrome (ACS), heart failure (HF), valvular disorders, stroke, rhythm disorders, and peripheral vascular disease.

ACUTE CORONARY SYNDROME

Chest Pain and Associated Symptoms

The most frequently reported symptom of ACS is chest pain. Chest pain has often been described as substernal pressure or discomfort and may radiate to the jaw, shoulder, arm, or upper back. The most common co-occurring symptoms with chest pain are dyspnea, diaphoresis, unusual fatigue, nausea, and lightheadedness.[16] Symptoms such as unusual fatigue and weakness have often been labeled as atypical in ACS, but this labeling may be a function of men being the standard for typical symptom presentation as opposed to true symptom frequency. In a review of 7 studies assessing prodromal symptoms of ACS,[17] chest discomfort/pain, arm pain/discomfort, jaw pain, back/shoulder blade pain, unusual fatigue, shortness of breath, sleep disturbance, dizziness, headache, anxiety, and gastrointestinal complaints were reported in ACS. Patients with persistent angina also experience higher rates of depression and anxiety.[18] It remains unknown how depression may affect the report of physical symptoms of ischemic heart disease; however, shortness of breath and chest pain may be more prevalent among depressed patients with ischemic heart disease.[19]

A central challenge in interpreting symptoms in ACS is the lack of consensus on the duration of the prodromal phase, which in the literature ranges from 1 month to 48 hours before an ACS event.[16,17] Women reporting arm pain or discomfort and unusual fatigue during initial ischemic heart disease evaluation are more likely to have a cardiac event at any point in the next 90 days.[20] However, few cardiac symptoms are actually sensitive and specific for ischemic heart disease. Consequently, women are at risk for additional morbidity such as sustaining an ST-segment–elevation myocardial infarction secondary to misjudging or attributing symptoms to a minor cause. Put simply, it can be challenging to determine whether prodromal symptoms are specific to an ACS episode, as well as their clinical relevance to patient outcomes.

Sex Differences

More similarities in symptom presentation in ACS have been reported among women compared with men, but salient differences have been found. For example, in the EPIHeart study, there were no significant differences in the frequency or location of chest pain by sex, but women reported significantly more severe pain and more referred pain compared with men.[21] In a large American cohort, women were significantly more likely to experience nausea, shoulder pain, upper back pain, and a greater number of ACS symptoms compared with men.[16] Last, in the VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients), younger women with acute myocardial infarction were more likely to present with a cluster of ≥3 symptoms (ie, epigastric symptoms, palpitation, and pain or discomfort in the jaw, neck, arms, or shoulders) compared with men.[12]

On average, women with ACS are significantly older than men, with differences ranging from 2 to 10 years.[16,21,22] Ischemic heart disease is less prevalent among women than men for every age group in the United States except 20 to 39 years of age.[23] The incidence of myocardial infarction or fatal ischemic heart disease is higher for women only after 85 years of age.[23] Younger individuals with ACS are more likely to be male, to smoke, and to have a family history of premature CVD. Younger adults are also less likely to have extensive disease or ST-segment–elevation myocardial infarction.[24] There is a caveat in that the term young varies across the literature, ranging from ≤40 to ≤55 years of age, and there is no universally accepted cutoff.[24] The contributions of chronological (passage of time) and biological (functional decline) aging[25] to symptoms experienced by patients with ACS are unknown.

Clinical Application of Measurement

A majority of ACS symptom measures are disease-specific and multidimensional, and many are valid and

reliable (Online Table).[26] However, the availability of multiple measures means that there is no standard instrument in use. A lack of standard measures means that there could be a bias in favor of certain symptom assessments and an inability to compare symptoms across cohorts. Moreover, lack of harmonization of ACS symptom measurement in research hampers growth in cumulative evidence. Therefore, little can be done to synthesize salient findings about symptoms across ischemic heart disease/ACS studies and to incorporate evidence-based information about symptoms into treatment guidelines and patient education materials. In clinical practice, tracking symptoms over time with respect to both severity and life interference with a valid and reliable measure would help contribute to the limited evidence base compared with the more typical arbitrary approaches to symptom appraisal. The Online Table outlines the strengths, limitations, and content of and key references for the various measures available for CVD.

HEART FAILURE

Dyspnea

Dyspnea (aka, shortness of breath, breathing discomfort, or breathlessness) is a hallmark of HF. Increased dyspnea is one of the most common reasons that adults with HF seek hospitalization, and severe dyspnea is associated with a greater risk of mortality.[27] Dyspnea is often characterized in terms of provocation, meaning dyspnea at rest, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and bendopnea.[28,29] It is important to account for dyspnea heterogeneity in both clinical practice and research by using nuanced measures and probing questions to capture this common and multifaceted symptom. Profiling techniques have been helpful in pinpointing patients with different clinical phenotypes of dyspnea in HF.[30] Moreover, it is important to consider non–HF-related causes when evaluating dyspnea, especially comorbid conditions such as chronic obstructive pulmonary disorder.[31]

Early Physical Symptoms

Early and subtle symptoms also can be harbingers of worsening HF and impending hospitalization or death.[27] For example, gastrointestinal-related symptoms such as upset stomach, nausea and vomiting, and loss of appetite can be related to intestinal congestion.[32] Fatigue is rated as both the most common and the most bothersome hallmark HF symptom.[33] Fatigue has variable causes both related and unrelated to HF pathophysiology and results in exercise intolerance, especially with co-occurring dyspnea. Together, these symptoms may herald muscle wasting and cachexia, which are indicators of HF progressing to more advanced stages.[34]

Other Symptoms and Symptom Clusters

Adults with HF commonly report insomnia and wake disturbances related to both HF (eg, pulmonary congestion) and non-HF causes (eg, sleep apnea), as well as side effects from medications (eg, nocturia).[35] Pain is a common but often unsolicited symptom in HF and can be attributable to cardiac causes (eg, deconditioning) or noncardiac causes (eg, diabetic neuropathy).[36] For some patients with HF, pain increases toward the end of life and can be exacerbated by physical limitations.[37] In addition to physical symptoms, 25% to 30% of adults with HF report mood disturbances, manifesting primarily as depressive and anxiety symptoms, that are independently associated with poor clinical outcomes.[38] In HF, physical and affective symptoms frequently cluster together regardless of cultural differences,[39] and such symptom clusters are associated with a gradient in clinical event risk.[13,40]

Cognitive dysfunction is common among patients with HF. It is likely attributable to lowered cerebral blood flow resulting from HF and associated with structural and functional changes to the brain.[41] A central challenge in dealing with cognitive dysfunction is that it is both a sign of HF and it directly affects a patient's ability to recognize and respond to other symptoms when they occur.[42] Accordingly, patients with HF who experience cognitive dysfunction have higher 30-day and 1-year mortality.[43] However, by definition, cognitive dysfunction is not subjective and is therefore not a symptom.

Sex and Age Differences

Women report higher physical symptom burden, higher depression and anxiety, and lower quality of life.[44–47] Symptoms reported more frequently by women are similar to what occurs in ACS (eg, nausea, palpitations, epigastric symptoms).[44,46] Women also were more likely to report higher pain (other than chest pain), nervousness, edema, and sweating.[44] Differences may partly be explained by a higher comorbid illness burden or diagnosis of HF at a later age among women.

Older adults in general perceive less dyspnea compared with younger adults.[48] Indeed, among adults with HF, older age is associated with problems recognizing and interpreting dyspnea.[49] In addition, physically frail adults with HF have significantly worse dyspnea, sleep-wake disturbances, and depressive symptoms compared with adults with HF who are not physically frail.[50] Taken together, both chronological age and biological age contribute to patient experience with symptoms in HF.

Clinical Application of Measurement

Several measures of symptoms in HF are commonly used and have evidence of validity and reliability (Online Table). Although quality of life and health status measures are

Table 2. Valve Lesions and Salient Symptom Differences

Aortic stenosis	AS may present with angina, syncope, or dyspnea, with none being specific for this disease.[52,54] All symptoms of AS portend progressive deterioration and limited survival. Mortality correlates with the presenting symptom, with angina being the least onerous; HF symptoms, notably dyspnea, carrying the worst prognosis; and syncope being in between.[55] Recommendation for delayed intervention in the absence of symptoms assumes that sudden cardiac death (that is, without antecedent symptoms) is rare in adults and is exceeded by surgical risk.[53] Intervention in severe disease is considered before symptom onset attributable to a decline in procedural morbidity and mortality and an estimated annual rate of sudden death between 0.5% and 1%.[53,54] Transcatheter aortic valve replacement has a favorable impact on symptoms and functional capacity in inoperable patients. It is at least equivalent to surgical intervention in high- to moderate-risk patients.[56,57]
Aortic regurgitation	Acute AR, as with acute bacterial endocarditis or acute aortic dissection, can be catastrophic, with acute pulmonary edema or cardiogenic shock. In chronic AR, after an often-protracted asymptomatic period, symptoms of HF reflect advancing LV remodeling and dysfunction. Early surgery is indicated when associated symptoms appear or in the presence of reduced LVEF (≤55%) to avoid progressive, irreversible LV damage.[52,53,58]
Mitral stenosis	With incident rheumatic MS virtually abolished, more cases are now recognized to be attributable to severe mitral annular calcification. Left-sided HF, with progressive dyspnea and exercise intolerance, is a manifestation of mitral flow obstruction, resulting in increased pulmonary vein pressure and impaired LV filling. Pulmonary hypertension, with associated RV dilation and dysfunction and symptoms of edema, hepatic congestion, and ascites, is more evident and less reversible with MS than with other valve lesions. Unlike with aortic valve disease, relatively mild symptoms may be manageable with diuresis and rate control. Advancing valve pathology and symptoms, including increased dyspnea and functional incapacity, call for mitral valvuloplasty or replacement.[53] Such intervention often results in dramatic symptom improvement and prevention of progressive symptoms of pulmonary arterial hypertension and right-sided HF.
Mitral regurgitation	MR may be functional, associated with LV and mitral annular dilation of any cause, or structural, with congenital or acquired valve deformity. Acute, severe MR often presents as acute pulmonary edema, which may require urgent intervention. In chronic MR, unlike aortic valve disorders, symptoms of left-sided HF result from direct LV ejection into the left atrium and therefore may occur in advance of significant LV damage. Mild symptoms may be manageable with diuretics, rate control, and vasodilators to reduce both LV afterload and preload. Factors affecting the decision for mitral repair or replacement include the severity and progression of symptoms, the nature of the valve lesion, the severity of regurgitant flow, and evidence for advancing LV dilation (end-systolic diameter ≥40 mm) and dysfunction (LVEF ≤60%).[53] Transcutaneous valve intervention for MR, in addition to reducing morbid and fatal events, has been shown to significantly improve health status.[59]
Tricuspid valve disease	Tricuspid stenosis is rare and results in symptoms of right-sided HF. Structural TR results from valve pathology, whereas TR is most commonly functional, associated with RV dilation attributable to myopathy, myocardial infarction, pulmonic valve obstruction, pulmonary emboli, or any other cause of pulmonary hypertension. TR symptoms are those of right-sided HF, including functional incapacity, edema, ascites, and hepatic congestion. In severe and chronic TR, hepatic failure may occur with its attendant symptoms, including jaundice, and may obviate procedures requiring general anesthesia. TR may be better tolerated when not associated with excessive RV afterload. Diuretics, pulmonary vasodilators, and nitrates often reduce symptoms of right-sided heart failure, particularly in functional TR. Structural intervention is considered in severe disease,[53] particularly in the case of valvular structural cause.

AR indicates aortic regurgitation; AS, aortic stenosis; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MS, mitral stenosis; RV, right ventricular; and TR, tricuspid regurgitation.

most commonly used in HF, the number of symptoms indirectly covered by such measures is limited. Current and future work in HF symptoms is now focused on symptom patterns and clustering over time, which have received limited attention in other CVDs.

VALVULAR HEART DISEASE

Valvular heart disease is a frequent cause of HF, with symptoms generally indistinguishable from other HF causes. Rheumatic heart disease, although still prevalent in low- and middle-income countries,[51] has largely disappeared elsewhere and has been replaced by population aging and cardiomyopathies as predominant drivers of valve disease. In the absence of acute severe valve dysfunction, patients generally have a prolonged asymptomatic period, followed by a period of progressive symptoms,[52] resulting from the valve lesion itself or secondary myocardial remodeling and dysfunction. The staging of valvular heart disease is based on a combination of valve findings, symptoms, and ventricular function.[53] Over time, left-sided valve dysfunction may result in pulmonary hypertension with tricuspid regurgitation and right-sided HF. Functional assessment may be aided by maximal exercise testing (ie, cardiopulmonary exercise testing). The 6-minute walk test and quality-of-life questionnaires are among the more common tools used to quantify benefit after valve intervention and to compare different interventional approaches. Among the valve lesions, there are subtle differences in terms of the role of symptoms in guiding the timing of intervention (Table 2).[56]

Sex Differences

Symptoms differ between the sexes for aortic valve disease. Aortic stenosis is typically asymptomatic for years. Women report dyspnea and exercise intolerance more often than men as stenosis progresses. Women also are more likely to be physically frail and to have a higher New York Heart Association class (III/IV) than men. Men are more likely to have chest pain.[60,61]

Clinical Application of Measurement

Symptom presence and severity are key in determining the stage of disease and timing of surgical or transcatheter intervention. However, the implication of symptoms differs across the various lesions. Quantitative symptom and functional assessments have been important research tools in gauging the efficacy of interventional treatment (Online Table). Given the importance of symptom assessment, more work is needed to determine the incremental value of quantitative symptom measurement as an aid to clinical management.

STROKE

Acute Stroke Symptoms

Acute symptoms often predict disability and quality of life after stroke.[62] Identifying and responding to stroke signs and symptoms quickly is essential for proper treatment.[63] Acronyms like FAST[64] (face, arm, speech, time) and related derivations were developed to facilitate lay public recognition and prehospital response to the most common signs of stroke. Weakness and numbness, speech problems, confusion, dizziness and loss of coordination/balance, and visual changes have been associated with the likelihood of seeking emergency care,[65,66] but timeliness of response differs by symptom.

For clinicians, classic stroke symptoms, in addition to nonclassic symptoms such as partial sensory deficit, dysarthria, vertigo, and diplopia,[67] require consideration for activating a stroke response team.[68] The Rapid Arterial Occlusion Evaluation Scale[69] and National Institutes of Health Stroke Scale show the best diagnostic accuracy values,[70] with the latter advocated for most because of rapid performance, along with both accuracy and reliability (Online Table).[71]

Poststroke Symptoms

After a stroke, acute symptoms may linger, becoming disabilities, or improve with time or rehabilitation. Although there are others, the Stroke Specific Quality of Life scale is the dominant means to assess physical function and is shorter and easier to administer in daily practice compared with alternatives.[72] Stroke severity, physical disability, and cognitive impairments after stroke are associated with common poststroke symptoms of anxiety, depression, fatigue, and pain.[73–76] About one-fourth of stroke survivors experience anxiety,[77] one-third experience depression,[75] at least half report fatigue,[78] and up to half report pain,[79] all at various stages in stroke recovery.

Sex Differences

A systematic review and meta-analysis revealed that women were more likely to present with nonfocal symptoms (eg, headache, altered mentality, and coma/stupor) than men.[80] To enhance public education about stroke symptoms and to facilitate the diagnosis and treatment of stroke, research is needed to better understand the presentation of stroke symptoms by other select demographic characteristics (eg, race and ethnicity, age, stroke subtype).

Clinical Application of Measurement

The significance of time is evident for when to assess stroke symptoms in the hyperacute and acute phases of stroke, but the optimal frequency of symptom assessment is less clear for the subacute and chronic phases. All people who experience a stroke should be screened for poststroke anxiety and depression and other physical and psychological issues (Online Table).[81] Stroke survivors at high risk of depression (eg, high stroke severity, age ≤50 years, history of depression, cognitive impairment) should be assessed at various stages throughout the continuum of stroke care, especially at transition points.[81] Although there are other means of assessing anxiety and depressive symptoms, in a systematic review, only the Hospital Anxiety and Depression Scale was recommended for its high sensitivity and specificity in stroke.[82] The 2016 American Heart Association/American Stroke Association "Guidelines for Adult Stroke Rehabilitation and Recovery" recommend the use of a structured depression inventory (eg, Patient Health Questionnaire-2) to routinely screen for poststroke depression.[83]

In a 2017 American Heart Association scientific statement on poststroke fatigue, the frequently used Fatigue Severity Scale was recommended.[73] Another tool, the Neurological Fatigue Index for Stroke, has been shown to screen fatigue at all levels of severity; it is easy to use and freely available from the authors.[84] It is recommended to assess for poststroke fatigue at discharge from acute care; at 3, 6, and 12 months; and then annually.[73]

Last, poststroke pain may involve neuropathic pain and nociceptive pain, musculoskeletal pains, shoulder pain, spasticity-related pain[76]; there are no stroke-specific measures of pain because of the heterogeneity of neurological deficits in this population.[79] Hence, general self-report questionnaires, pain scales, and

clinical assessment are used to assess poststroke pain. Poststroke pain can take weeks to months to develop, with the highest prevalence rates at 4 to 6 months.[79,85] Prevalence rates and individual responses should guide the assessment of pain and anxiety after stroke.

RHYTHM DISORDERS

Cardiac arrhythmias, including atrial fibrillation (AF), atrial flutter, supraventricular tachycardias, bradyarrhythmias, and ventricular tachycardia, present with common symptoms. Palpitations (ie, perceiving the heartbeat as irregular, rapid, fluttering, skipping, or pausing) is a characteristic symptom of many cardiac arrhythmias. The most common cardiac arrhythmia, AF, may present with palpitations or less specific symptoms (eg, fatigue, dyspnea, dizziness) that occur in association with a broad range of disease conditions.[86] Palpitations are considered the typical symptom presentation for AF, yet patients with new-onset AF often present either asymptomatically or with nonspecific symptoms.[86] Palpitations (27%–70%), fatigue (26%–75%), and dyspnea (28%–76%) are the most common symptoms reported by patients with AF, whereas chest pain (12%–30%), dizziness (19%–44%), presyncope/syncope (3%–4%), and anxiety (12%–50%) occur less frequently.[87–90] Psychological distress also may be associated with worse AF symptom severity.[91] Last, AF symptoms do not correspond to objectively measured AF episodes in all cases.[92] Even within the same individual, AF may fluctuate between symptomatic and asymptomatic.[93]

Tachycardia accounts for some symptom variability, although achieving heart rate control does not always eliminate symptoms.[94] AF ablation reduces symptoms,[95] but the effect is not attributable solely to a reduction in AF burden. It is interesting to note that in 1 study 52% of AF episodes were asymptomatic before AF ablation and 79% were asymptomatic after ablation.[96] AF also is a well-known risk factor for developing stroke and dementia.[97] Moreover, even among patients without prior stroke, the diagnosis of AF is a risk factor for poor cognitive function.[98] Symptoms of AF are often erroneously attributed to deconditioning, stress, or sleepiness, leading to delays in seeking medical attention for a week or longer.[99] Nonspecific (fatigue and dyspnea) and intermittent symptoms are associated with a delay in seeking treatment for AF, whereas cardiac-specific symptoms, including palpitations and chest pain, are not.[100] In a longitudinal cohort, patients with AF who initially presented with palpitations had lower stroke and mortality rates, even after adjustment for thromboembolic risk and anticoagulation.[86] In ORBIT-AF (Outcomes Registry for Better Informed Treatment of AF)[101] and RACE II (Rate Control Efficacy in Permanent AF),[102] worse AF symptom severity was associated with higher hospitalization rates. Symptoms also are the reason for presentation in 50% of patients presenting to the emergency department for AF.[103]

Sex, Age, and Racial Differences

Women and younger individuals with AF typically present with palpitations,[14,86] whereas men are more commonly asymptomatic.[86,104,105] Older age also increases the likelihood of a nonclassic or asymptomatic presentation of AF.[14,86,105] With regards to race, 2 systematic reviews reported an AF paradox in terms of symptoms associated with AF. Despite non-Hispanic Black individuals being at lower risk for development of AF, Black patients are burdened more with palpitations, dyspnea on exertion, exercise intolerance, dizziness, dyspnea at rest, and chest discomfort compared with White or Hispanic patients.[106,107]

Clinical Application of Measurement

Symptom monitoring and the association between symptoms and heart rate and rhythm are essential components of medication titration for rate control and selection of a rate versus rhythm control management strategy.[108] Clinicians underrepresent AF symptom severity[102]; hence, clinician-reported AF symptom measures should be avoided unless absolutely necessary. Several measures are available to quantify rhythm disorders; however, some are limited in terms of validity testing or comprehensiveness of symptoms assessed (Online Table). Correlating symptoms and rhythm also can present a challenge when symptoms occur infrequently and unpredictably, but mobile health devices increase AF detection compared with standard practice (eg, mobile devices, in-office ECGs, 24-hour Holter) and therefore reduce diagnostic delay and improve symptom-rhythm correlation.[109]

PERIPHERAL VASCULAR DISEASE

Peripheral Arterial Disease

Peripheral vascular disease and its associated symptoms can arise from either arterial or venous pathology. Peripheral arterial disease (PAD) is a progressive atherosclerotic disease resulting in insufficient blood flow to the lower extremities. PAD symptoms vary, ranging from none (despite disease progression) to leg pain at rest. Classic claudication occurs in approximately one-third of patients and is defined as calf pain that occurs in 1 or both legs with exertion (walking), does not begin at rest, and resolves within 10 minutes of standing still or rest. Nonclassic symptoms (eg, noncalf exercise pain) are reported more frequently than classic claudication symptoms. Assessing symptoms at rest, during exercise, and during recovery can assist with classifying symptoms as ischemic or not.[110,111]

Table 3. Common Symptoms Across CVD Diagnoses

Anxiety	Chest pain	Depression	Dizziness	Dyspnea	Fatigue
ACS	ACS	ACS	AF	ACS	ACS
AF	Aortic stenosis	HF	Stroke	Aortic stenosis	AF
HF	AF	PAD		AF	HF
Stroke		Stroke		HF	PVD
					Stroke

ACS indicates acute coronary syndrome; AF, atrial fibrillation; CVD, cardiovascular disease; HF, heart failure; PAD, peripheral arterial disease; and PVD, peripheral venous disease.

Limb ischemia is the most severe form of PAD, with individuals experiencing pain in their legs, feet, or toes. Symptomatic PAD is associated with an increased risk of major adverse cardiovascular events, with men at higher risk.[112,113] Last, depression is common in PAD, with a prevalence (3%–48%) similar to that of other types of CVD. Women, the elderly, individuals of underrepresented races and ethnicities, and those with worse disease and physical function are at increased risk of depression.[114]

Peripheral Venous Disease

Similar to patients with PAD, individuals with peripheral venous disease (PVD) can be symptomatic or asymptomatic. Clinical classification of PVD includes symptoms such as leg pain, aching, fatigue, heaviness, cramping, tightness, restless legs syndrome, and skin irritation. In a study of symptoms in chronic venous disorders (n=38 750; 78% female), pain, heaviness, aching, and fatigue were more common in people <65 years of age.[115] Pain and heaviness are believed to be caused by venous dilatation and hypoxia of the venous wall.[115,116] Symptoms also may occur without visible signs of PVD.

Sex Differences

Sex differences in peripheral vascular disease are specific to PAD. Women with PAD are more likely to have nonclassic symptoms or an absence of symptoms. Symptom attribution among women is complicated by comorbid musculoskeletal diseases (eg, osteoarthritis) or the mistaken belief that PAD is more common in men. Women with PAD also have a more rapid decline, worse quality of life, and higher burden of depression.[117]

Clinical Application of Measurement

Existing measures for PVD are quality-of-life measures that include symptoms, limitations of activities of daily living, and psychological impact (Online Table). Current PVD measures have limitations similar to other CVDs in terms of data supporting responsiveness to change or minimally important differences. Moreover, existing legacy measures of PVD are centered on clinician appraisal versus patient-reported symptoms.

CONCLUSIONS

Amelioration of CVD symptoms is an integral part of CVD management. It is important to recognize that CVD symptoms are simply not static and may vary in occurrence or severity over time. Moreover, several symptoms such as dyspnea and fatigue are common across disorders. Therefore, it is prudent to use established measures or to develop reliable, valid, relevant, and responsive measures of CVD symptoms for tracking over time. It is important to acknowledge that several existing measures have limitations in terms of responsiveness to change or lack of established minimally important differences. Most measures have not been evaluated for measurement error based on sex, race, or ethnicity, which is problematic given the lack of sex balance and racial representation in CVD research. Many measures are used on the basis of legacy application versus appropriateness for informing research or clinical care. Monitoring symptoms with reliable and valid measures in research and clinical practice may enhance clinical care by identifying those who may be at risk for poor outcomes more quickly (eg, lower quality of life, hospitalization, death).

People living with CVD commonly have symptoms directly related to their CVD and their other chronic conditions, as well as associated symptoms such as sleep disturbance and depression (Table 3). Therefore, it is challenging for people living with CVD to disambiguate and appropriately attribute their symptoms to any one disorder. Furthermore, cognitive dysfunction and depression have a bearing on patients' ability to detect underlying changes in symptoms[42,118–120]; therefore, both should be measured to establish a baseline and in response to significant clinical changes. More information is needed on the relationship between symptoms and clinical events, as well as underlying CVD pathogenesis, especially among people living with multiple chronic conditions. Despite limitations in measurement and complexities in how they are experienced, symptoms have clear relevance to the diagnosis, monitoring, and treatment of CVD.

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The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a

Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Corrine Y. Jurgens	Boston College School of Nursing	None	None	None	None	None	None	None
Christopher S. Lee	Boston College	NIH (MPI/co-I)†; PCORI (DSMB chair)*	None	None	None	None	None	None
Dawn M. Aycock	Georgia State University	Gordon and Betty Irene Moore Foundation (funded grant)†	None	None	None	None	None	None
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Holli A. DeVon	University of California Los Angeles School of Nursing	None	None	None	None	None	None	None
Linda R. Evers	Linda Evers, Stevens & Lee	None	None	None	None	None	None	None
Miyeon Jung	Indiana University School of Nursing	AHA (PI)†; NIH/NINR (co-I)†; Indiana University School of Nursing (PI)*; Midwest Nursing Research Society (a mentor on a dissertation grant)*	None	None	None	None	None	None
Marvin A. Konstam	Tufts Medical Center, The CardioVascular Center	None	LivaNova†; scPharma† (all clinical trials)	None	None	None	Boehringer Ingelheim†; Carduriant†; Cytokineticst; LivaNova†; Luitpold*; Merckt; Pfizert; scPharma†	None
Ruth Masterson Creber	Weill Cornell Medicine	None	None	None	None	None	None	None
Gianluca Pucciarelli	University of Rome Tor Vergata (Italy)	None	None	None	None	None	None	None
Megan M. Streur	University of Washington	NIH/NINR (K23NR017632 [PI])†	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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Jonathan Auld	University of Washington	National Institute of Nursing Research (K23 award)†	None	None	None	None	None	None
Kenneth M. Faulkner	Stony Brook University	None	None	None	None	None	None	None
Lisa Kitko	Penn State University	None	None	None	None	None	None	None
Lea Ann Matura	University of Pennsylvania	Bayer (funding for an RCT to treat [nonpharmacologically] insomnia and fatigue)†	None	None	Peter A. Allegra*	None	None	None
Bunny J. Pozehl	University of Nebraska Medical Center	None	None	None	None	None	None	None
Jessica H. Thompson	University of Kentucky	NIH (K award–BIRCWH recipient, fellow, University of Kentucky)*	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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