Original Research Article

Screening for Vascular Disease in Pulmonary Rehabilitation

ABSTRACT

Background: Several of the comorbidities and risk factors associated with COPD and other pulmonary disorders are also similar to those for lower extremity peripheral artery disease (PAD) and cerebrovascular disease. The later condition is often manifested as cognitive impairment, not only from large vessel associated stroke, but also from vascular cognitive impairment (VCI). We hypothesized that pulmonary rehabilitation (PR) would be an appropriate site to discern the prevalence of both PAD and mild cognitive impairment (MCI).Individuals in PR with severe pulmonary disease may have impaired cognition, which could impact learning and treatment adherence while PAD may contribute to functional limitation.

Study Design: In this pilot study of 14 patients enrolled in phase II PR, we describe the prevalence of PAD and cognitive impairment, the utility of screening tools, and the potential relationship between PAD, depression, and cognitive impairment.

Results: Twenty-eight percent of patients had an abnormal ABI with two subjects manifesting low (< 0.90) and two subjects with abnormally high (>1.40) ABI. The Edinburgh Claudication Questionnaire was negative in all subjects and was not useful in the detection of PAD (sensitivity 0%, specificity 11%, PPV 0%, NPV 78.57%.) The Walking Impairment Questionnaire did not differentiate patients with or without abnormal ABIs with respect to walking distance (40.02 vs. 64.46 meters, *P*= .154), speed (27.15 vs. 25.92 miles per hour, *P*=.545), or symptoms (46.88 vs. 63.75, *P*= .152). Furthermore, eleven of the fourteen patients (79%) had an overall score of less than 26 on the Montreal Cognitive Assessment, indicating cognitive impairment. Scores indicating mild to moderate depression or anxiety measured by the PHQ-9 and STAI questionnaires revealed a concurrence between depressive and anxiety symptoms.

1. INTRODUCTION

Pulmonary disorders are an increasing cause of disability and functional impairment, followed by high rates of mortality. [1] Patients enrolled in a pulmonary rehabilitation (PR)

21 program are provided with individually tailored therapy to minimize their disability, to improve
22 functional impairment and disease specific knowledge, and to decrease the psychological
23 burden of their disorder. A majority of patients enrolled in PR are diagnosed with chronic
24 obstructive pulmonary disease (COPD), the fourth-leading cause of death in the United
25 States. [1] Several of the co-morbidities and risk factors associated with this and other
26 pulmonary disorders are notably similar to those for lower extremity peripheral artery disease
27 (PAD) and cerebrovascular disease. Symptomatic and functional consequences of PAD
28 emerge from intermittent or chronic leg ischemia leading to claudication. Cerebrovascular
29 disease is often manifested as cognitive impairment, not only from large vessel associated
30 strokes, but also from vascular cognitive impairment (VCI).   This latter condition is a
31 heterogeneous group of disorders including VCI-no dementia, vascular dementia, and
32 cognitive impairment of mixed (Alzheimer's disease and vascular dementia) origin. [2]
33 Additionally, patients with VCI-no dementia have a high risk of progression to dementia,
34 mixed primary neurodegenerative dementia, and vascular dementia, particularly if they have
35 recurrent strokes. [2] Furthermore, structured lower extremity exercise is the fundamental
36 component of treatment for claudication, and there is an increasing amount of evidence
37 affirming that it may result in improvement of cognitive dysfunction. [3] Therefore, we
38 hypothesized that PR would be an appropriate site to discern the prevalence of both PAD
39 and mild cognitive impairment (MCI), as well as potentially to administer therapeutic
40 interventions targeted to improve both vascular maladies.
41
42 PAD is often undetected and untreated, despite the high prevalence of this disease and its
43 significant clinical consequences. [3] The ankle-brachial index (ABI) is a widely used non-
44 invasive and cost effective test for screening, which compares the higher of the brachial
45 artery systolic blood pressures with both the left and right lower extremities (either the
46 *dorsalispedis* or *posterior tibial*) systolic blood pressure in a simple ratio. [4] Standardized
47 questionnaires, validated in settings other than PR have been used as well. The Edinburgh
48 Claudication Questionnaire is one such questionnaire that has been validated as a PAD
49 screening tool with reported 91% sensitivity and 99% specificity for diagnosis in the general
50 populations. [5] Additionally, the Walking Impairment Questionnaire is another validated
51 method that assesses functional limitations by helping identify the degree of walking ability in
52 the PAD populations in comparison to graded treadmill tests. [6]
53
54 Cognitive impairment is increasingly recognized as common in many medical conditions and
55 may relate to the ability of the cardiovascular system to provide adequate brain perfusion.
56 Reduced cerebral blood flow and structural brain changes including greater global and
57 region-specific atrophy are often implicated, as past work in patients with COPD or
58 depression has demonstrated a strong relationship between cognitive dysfunction and
59 decreased fitness in patients with COPD or depression [7].   Specifically, the recent
60 Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study concluded that midlife
61 COPD and asthma were associated with an almost two-fold risk of mild cognitive impairment
62 and dementia later in life [8]. Therefore, it may be hypothesized that individuals in PR with
63 severe pulmonary disease may have impaired cognition, and this especially may be the case
64 with those diagnosed with vascular diseases such as PAD.
65
66 **2. MATERIALS AND METHODS**
67
68 **2.1 Goals**
69 The primary goal of this study was to determine the validity of screening tools in detecting
70 PAD in comparison to ABI status in a representative population of patients in pulmonary
71 rehabilitation. Secondary goals included the detection of cognitive impairment (defined by
72 standardized neuropsychological testing with the Montreal Cognitive Assessment, MoCA)

73 and of depression. Thus, we sought to find a quantitative relationship between these
74 important medical conditions.

76 **2.2 Protocol**

78 This was a prospective observational pilot study of 25 consecutive subjects enrolled in
79 phase II PR at University Hospitals Harrington Heart & Vascular Institute's Pulmonary
80 Rehabilitation Program in Ohio. All patients enrolled in PR between June 21, 2013 and
81 August 27, 2013 were considered for this study. Exclusion criteria included individuals with
82 required use of an assistive device (walker, cane, or wheelchair) for ambulation (n=2),
83 documented dementia (n=0), or failure to provide informed consent (n=10).

84 The research assistant screened subjects for the study during the course of the patients'
85 rehabilitation sessions. If the subject met the selection criteria, informed consent was
86 obtained the day of screening or at the following session.

87 The study was conducted with minimal interruption to the course of pulmonary rehabilitation.
88 After consent was obtained, the Walking Impairment Questionnaire, the Edinburgh
89 Claudication Questionnaire, and the Seton Medical Center Pulmonary Knowledge Test were
90 administered. Following the first set of questionnaires, the research assistant obtained ABI
91 measurements according to the American Heart Association recommendations. [9]At the
92 next scheduled rehabilitation session, the following surveys were administered: the Montreal
93 Cognitive Assessment (MoCA), the State Trait Anxiety Inventory, and the Patient Health
94 Questionnaire 9 (PHQ-9), which were used to screen for anxiety and depression symptoms
95 respectively.

97 **2.3 Data Analysis**

99 The prevalence of peripheral artery disease, defined as an ABI <0.9 or >1.4 was described
100 for the overall study population. Baseline characteristics of subjects with abnormal ABI were
101 compared to those subjects with normal ABI. Furthermore, continuous variables were
102 reported with standard descriptive statistics including mean and standard deviation.
103 Between-group differences were tested for statistical significance with an unpaired t-test,
104 and categorical variables were described as frequency and percentage. The test
105 characteristics of the Edinburgh Claudication Questionnaire for the detection of abnormal
106 ABI in this population were described in terms of sensitivity, specificity, and negative and
107 positive predictive value. Unpaired t-tests were used to compare the walking ability scores
108 on the Walking Impairment Questionnaire of patients with normal ABI to those with abnormal
109 ABI. Additionally, the prevalence of depressive symptoms, assessed by PHQ-9, was
110 described as percentages. Similarly, the overall scores on the MoCA were compared
111 between both groups by percentages. The pulmonary knowledge of the rehabilitation
112 patients was related with standard descriptive statistics. Lastly, the results of the MoCA
113 were correlated with those of the PHQ-9 and STAI questionnaires using chi-square testing
114 and two sample t-tests. All statistical tests were two-sided with a 0.05 significance level.
115 Analyses were performed with SPSS version 20 (IBM SPSS Statistics for Windows, Armonk,
116 NY).

117 **3. RESULTS**

119 **3.1 Patient Population**

121 Twenty-five consecutive patients enrolled in phase II pulmonary rehabilitation were assessed
122 for eligibility and all met criteria; 8 were not consented within the first six exercise sessions

123 and 17 agreed to participate however 3 did not complete testing due to early withdrawal from
124 the program.

125 The prevalence of PAD in this population of PR patients was 28% (4/14), with two subjects
126 manifesting low (< 0.90) and two subjects with abnormally high (>1.40) ABI.(Figure 1)
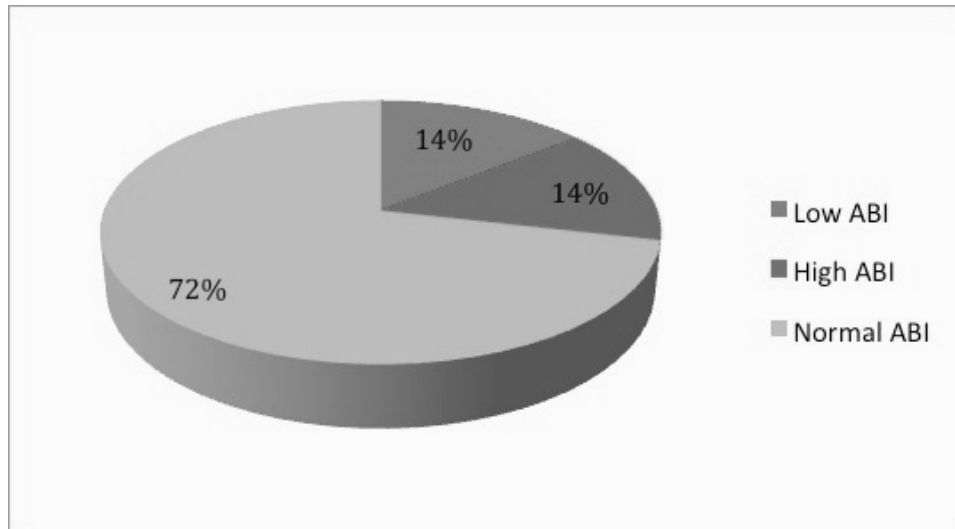
127

128 **Fig. 1.Prevalence of PAD in PR**
129 *PAD= Peripheral Artery Disease; PR= Pulmonary Rehabilitation*
130
131 Table 1 contains the baseline characteristics of subjects with normal ABI compared to those
132 with abnormal ABI as well as risk factors for PAD.

133 **Table 1.Baseline Characteristics and Risk Factors for PAD in Both ABI Groups**
134 *DM=; Diabetes Mellitus HTN= Hypertension; DLD= Dyslipidemia; COPD= Chronic Obstructive*
135 *Pulmonary Disorder; OA= Osteoarthritis*
136

Demographic	Normal ABI	Abnormal ABI
Number	10 (72%)	4 (28%)
Age	66 (+/- 7.5)	66.8 (+/- 12.8)
Sex		
Male	4 (28.6%)	2 (14.3%)
Female	6 (42.8%)	2 (14.3%)
Race		
African American	5 (35.7%)	2 (14.3%)

White	5 (35.7%)	2 (14.3%)
BMI (kg/$\frac{white}{m^2}$)	32.3 (+/- 9.2)	30.4 (+/-12.6)
Past Medical History		
PAD	0	0
DM	2 (20%)	0
HTN	4 (40%)	3 (75%)
DLD	1 (10%)	1 (25%)
COPD	10 (100%)	2 (50%)
Asthma	2 (20%)	1 (25%)
OA	6 (60%)	2 (20%)
Smoking History		
Current/Former	9 (90%)	4 (100%)
Never	1 (10%)	0

137
138 **3.2 Risk Factors**
139
140 The total number of traditional risk factors for PAD was assessed in both groups, including
141 the presence of smoking history, diabetes, obesity (BMI>30), hypertension, dyslipidemia,
142 and age >50. Most of the patients in each PR group displayed at least three risk factors,
143 however there was no statistically significant difference between the average numbers of risk
144 factors when comparing subjects with normal ABI to those with abnormal ABI (P= .465).

145 **3.3 Edinburg Claudication Questionnaire (ECQ)**
146
147 The Edinburgh Claudication Questionnaire performed poorly in this population of PR
148 patients, as it was negative in all subjects. Therefore, it was not useful in the detection of
149 PAD in this population. (sensitivity 0%, specificity 11%, PPV 0%, NPV 78.57%.)

150 **3.4 Walking Impairment Questionnaire (WIQ)**
151
152 The WIQ also performed poorly in this population, as it did not correlate with the presence of
153 PAD. The questionnaire did not reveal any differences between patients with abnormal
154 compared to normal ABIs with regard to walking distance, speed, or symptoms. (Table 2;
155 P=.154, P=.545, P=.152)

156 **Table 2.Average Results on the WIQ between Patients withAbnormal and Normal ABIs**
157 *ABI= Ankle-Brachial Index*
158

Section	Abnormal ABI (average score)	Normal ABI (average score)	P-value
Walking Distance (m)	40.015	64.456	0.154
Walking Speed (mph)	27.15	25.92	0.545
Walking Symptoms	46.875	63.75	0.152

159
160 **3.5 Montreal Cognitive Assessment (MoCA)**
161
162 Eleven of the fourteen patients (79%) had an overall score of less than 26, indicating
163 cognitive impairment. One of the three patients who scored >26 had an abnormal ABI.
164 Among the sub-scores, lowest performances were found in abstraction, delayed recall, and
165 visuospatial/executive skills, in which 9 of 14 patients completed the alternating trail making
166 incorrectly. Even with a high proportion of patients scoring less than 26, there was not
167 statistically significant evidence of a relationship between low scores and patients with
168 abnormal ABIs (*P*=.837). (Figure 2)
169
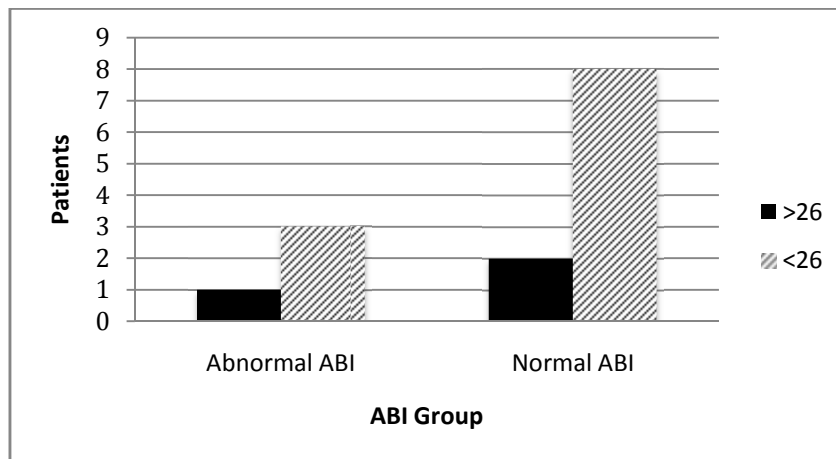
170
171
172 **Fig. 2.MoCA Results of Patients with Abnormal and Normal ABIs**
173 *Scores >26 considered normal*
174
175 **3.6 Seton Knowledge Test**
176 The mean score on the Seton Knowledge test in this population was a 19/25 (76%), which
177 would be considered average performance. Six patients scored 19 points or below, whereas
178 8 patients scored 20 or above. There was a large range of scores with a minimum of 11 and
179 a maximum of 24. Of the six patients with scores 19 or less, all scored <26 on the MoCA,
180 five scored minimal to mild depression on the PHQ-9, and five scored low to moderate state
181 anxiety on the STAI. Moreover, half of the six patients had abnormal ABIs. (Figure 3)
182
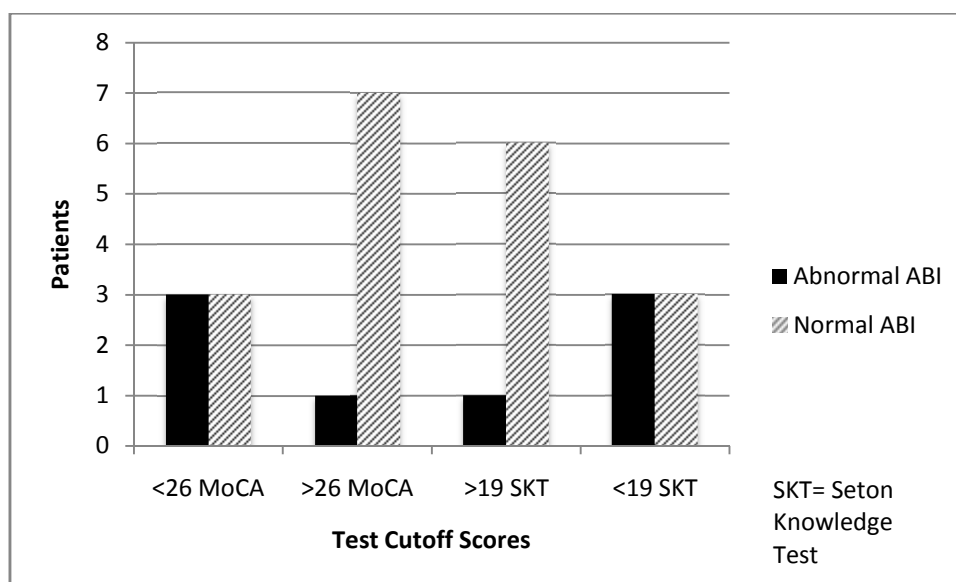
Fig. 3.Performance on the MoCA& Seton Knowledge Test Amongst Both ABI Groups

3.7 STAI/PHQ-9

Most patients' scores correlated to moderate state anxiety on the STAI questionnaire and similarly, those of the PHQ-9 corresponded with none, minimal, or mild depression. Although, one patient scored moderate to severe state anxiety and another scored moderate depression. Three of the four patients with abnormal ABIs that scored low to moderate on the STAI, and minimal to mild depression on the PHQ-9, had an overall score of <26 on the MoCA. Similarly among patients with normal ABIs, 9 of 10 patients that scored none to moderate on the PHQ-9, scored <26 on the MoCA. Despite this trend, there was not a statistically significant correlation with depression and anxiety levels and results of the MoCA among both patient groups (*P*=.466, *P*=.075).

4. DISCUSSION

4.1 Screening for Occult Peripheral Artery Disease

PAD is prevalent in patients with known cardiovascular disease as reported in previous studies, [2] however little is known about its relation to pulmonary disease and its prevalence in the pulmonary rehabilitation population. This study confirms and updates prior studies indicating that lower extremity PAD is prevalent in the pulmonary rehabilitation population. Despite the ability of the Edinburgh Claudication Questionnaire and other screening modalities to detect PAD in the general population, they are less sensitive in the PR population. These patients are likely to have other functionally limiting co-morbid conditions that may mask the presence of typical claudication symptoms, confounding the clinical detection of PAD. Additionally, selective screening based on risk factor stratification is of limited value in the PR population. As a result, this supports the application of ABI as a simple screening test for all patients enrolled in PR to detect PAD, as many patients are asymptomatic or have atypical symptoms.

217
218 **4.2 Prevalence of Mild Cognitive Impairment**
219
220 Cognitive impairment is prevalent in our representative PR population. It has been found that
221 patients with Vascular Cognitive Impairment (VCI) even if they do not have lesions on
222 neuroimaging can have a notably poor prognosis.[2] Additionally, lower scores on the Seton
223 Knowledge test could be related to below normal scores on the MoCA, as all six patients that
224 answered 19 or fewer questions correctly out of 25 on the Seton Knowedge test also scored
225 lower than 26 on the MoCA. Half of these patients had abnormal ABIs. This may reflect an
226 inability to retain information learned in rehabilitation sessions as a consequence of MCI. As
227 a result, there is an emerging concurrence between PAD and cognitive impairment.

228 **4.3 Prevalence of Depressive and Anxiety Symptoms**
229
230 Past prospective studies have found that depressive symptoms are associated with cognitive
231 decline and that the effect of anxiety on cognitive function is indirectly mediated by
232 depression [10]. Thus, the established relationship between cognitive impairment and
233 depression can be taken into consideration amongst patients with PAD, who have markedly
234 reduced health-related quality of life and higher prevalence of depression. [11] The
235 association between depressive symptoms and reduced cognitive function can be explained
236 by the ruminative processing of negative information that may reduce effort and attention to
237 demanding cognitive tasks. [10] Furthermore, depression in patients with cognitive
238 impairment is marked by abnormalities on neuropsychological tests including impairments in
239 memory, attention, and executive function [12], all of which are assessed in the MoCA.
240 Consequently, our results affirm the existing relationship between depressive and anxiety
241 symptoms and cognitive impairment, and also allude to a relationship between PAD and
242 depression and anxiety.
243
244 **5. STUDY LIMITATIONS AND IMPLICATIONS**
245
246 PAD was defined in our study by abnormal ABI. Other less common but more sophisticated,
247 costly, and often higher risk diagnostic methods such as pulse volume recording, computed
248 tomography angiography, and magnetic resonance angiography were not utilized given
249 financial and logistical restrictions. Furthermore, this pilot study was limited by the small
250 sample size, making it difficult to correlate MoCA scores with results of the PHQ-9 and the
251 STAI among patients with abnormal and normal ABIs.

252 As the prevalence of PAD is common in both pulmonary and cardiac rehabilitation [13],our
253 study extends other work for future studies assessing MCI in a larger PR population.
254 Furthermore, inquiry into the prevalence of MCI in patients with PAD would be of great
255 significance as well considering both of their clinical consequences. In a population- based
256 study, progression from VCI-no dementia to incident dementia occurred at the highest rate in
257 patients with both memory and functional impairment at baseline. Equivalently, up to a third
258 of people change diagnostic category (no cognitive impairment; cognitive impairment-no
259 dementia; dementia) within one year after stroke. [2] Therefore, cognitive impairment has
260 become increasingly common and debilitating, and should be a target for further study in the
261 proposed populations.

262 **6. CONCLUSIONS**
263
264 PAD is common in patients in phase II pulmonary rehabilitation and is often clinically occult.
265 It is infrequently detected by standard screening questionnaires in this population,

266 suggesting a need for a broad-based screening strategy including ABI measurements. In
267 fact, unappreciated PAD may correlate with mild cognitive impairment, which was observed
268 in a significant percentage of patients. Overall, our results have affirmed the substantial
269 prevalence of both PAD and cognitive impairment in PR. We found a positive correlation
270 between low Seton Knowledge test scores and low MoCA results, indicating the lack of
271 acquisition of disease related knowledge, which is one of the primary goals of PR. The
272 concurrence between depressive and anxiety symptoms and cognitive impairment was
273 affirmed as well. Individuals with depression have a greater tendency to submit to unhealthy
274 habits and risks, which may lead to increasing the risks of cardiovascular disease, cognitive
275 impairment, or worsening existing conditions. [12] Therefore, our conclusions have leaded
276 us to postulate a possible relationship between PAD and MCI, along with that of PAD and
277 depression and anxiety. Future studies, with a large sample size, will provide more insight on
278 ameliorating care for patients whose vascular disease affects cognitive function and mental
279 health.

280
281
282 **CONSENT**
283
284 All authors declare that 'written informed consent was obtained from the patient (or other
285 approved parties) for publication of this case report and accompanying images. A copy of
286 the written consent is available for review by the Editorial office/Chief Editor/Editorial Board
287 members of this journal.
288
289 **ETHICAL APPROVAL**
290
291 All authors hereby declare that all experiments have been examined and approved by the
292 appropriate ethics committee and have therefore been performed in accordance with the
293 ethical standards laid down in the 1964 Declaration of Helsinki.
294
295 **REFERENCES**
296

297 1.   Pulmonary Rehabilitation Executive Summary*: Joint American College Of Chest
298 Physicians/American Association Of Cardiovascular And Pulmonary Rehabilitation
299 Evidence-Based Clinical Practice GuidelinesRies AL, Bauldoff GS, Carlin BW, et al.*Chest*.
300 2007;131(5_suppl):1S-3S.

301 2. Moorhouse, P., & Rockwood, K. (2008). Vascular cognitive impairment: Current
302 concepts and clinical developments. *Lancet Neurology*, 7, 246-255.

303 3. Hamburg NM, Balady GJ. Exercise rehabilitation in peripheral artery disease: functional
304 impact and mechanisms of benefits. Circulation. 2011 Jan 4; 123(1): 87-89.

305 4. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA
306 2005 Practice Guidelines for the management of patients with peripheral arterial disease
307 (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the
308 American Association for Vascular Surgery/Society for Vascular Surgery, Society for
309 Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology,
310 Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines
311 (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral
312 Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary
313 Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing;

314   TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation.Circulation. 2006
315   Mar 21;113(11):e463–654.

316   5. Leng GC, Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version
317   of the WHO/Rose Questionnaire for use in epidemiological surveys. J. Clin. Epidemiol.1992
318   Oct; 45(10): 1101-9.

319   6. Sagar SP, Brown PM, Zelt DT, Pickett WL, Tranmer JE. Further clinical validation of the
320   walking impairment questionnaire for classification of walking performance in patients with
321   peripheral artery disease. Int. J. Vasc. Med. 2012;2012:190641.

322   7.   Garcia S, Alosco M-L, Sptiznagel M, et al.   Cardiovascular fitness associated with
323   cognitive performance in heart failure patients enrolled in cardiac rehabilitation.   BMC
324   CardiovascDisord. 2013; 13: 29.

325   8.   Rusanen N, Ngandu T, Laatikainen T, Tuomilehto J, Soininen H, Kivipelto M. Chronic
326   Obstructive Pulmonary Disease and Asthma and the Risk of Mild Cognitive Impairment and
327   Dementia: A Population Based CAIDE Study. Current Altzheimer Research. 2013; 10:
328   549-555.

329   9. Measurement and Interpretation of the Ankle-Brachial Index: A Scientific Statement From
330   the American Heart Association. Circulation.2012**;** 126: 2890-2909.

331   10. Pietrzak RH, Maruff P, Woodward, M, Fredrickson, JB, Fredrickson AB, Krystal, JH,
332   Southwick, SM, Darby, D. Mild Worry Symptoms Predict Decline in Learning and Memory in
333   Healthy Older Adults: A 2-Year Prospective Cohort Study. American Journal of Geriatric
334   Psychiatry.Vol. 20(3), p.266-275, Mar. 2012.
335

336   11. McDermott MM, Guralnik JM, Ferrucci L, Tian L, Liu K, Liao Y, et al. Asymptomatic
337   peripheral arterial disease is associated with more adverse lower extremity characteristics
338   than intermittent claudication. Circulation. 2008 May 13;117(19):2484–91.

339   12. Sohani ZN, Samaan Z. Does Depression Impact Cognitive Impairment in Patients with
340   Heart Failure? Cardiology Research and Practice. Vol. 2012.
341   13. Marty C. Tam, Richard Sukeena, Chen H. Chow, Chris T. Longenecker, Marianne Vest,
342   Sri Krishnan Madan Mohan, Teresa Carman, Sahil A. Parikh, Richard A. Josephson,
343   Peripheral Arterial Disease Worsens Outcomes for Patients in Cardiac Rehabilitation.
344   Journal of Cardiopulmonary Rehabilitation and Prevention, Vol. 33, No. 5., p. 339, Sept.
345   2013.
346
347
348
349

350