Available online: www.notulaebiologicae.ro
Print ISSN 2067-3205; Electronic 2067-3264
Not Sci Biol, 2017, 9(4):473-479. DOI: 10.15835/nsb9410168
Original Article

Evaluation of Patients with Lower Extremity Peripheral Artery Disease by Walking Tests: A Pilot Study

Andra CIOCAN[1], Răzvan A. CIOCAN[2], Claudia D. GHERMAN[3,4], Sorana D. BOLBOACĂ[2*]

[1]*University of Medicine and Pharmacy "Iuliu Haţieganu", Cluj-Napoca, Romania; ciocan.andra@yahoo.com*
[2]*University of Medicine and Pharmacy "Iuliu Haţieganu", Department of Medical Informatics and Biostatistics, Cluj-Napoca, Romania; Razvan.Ciocan@umfcluj.ro; sbolboaca@umfcluj.ro (*corresponding author)*
[3]*University of Medicine and Pharmacy "Iuliu Haţieganu", Department of Ability and Human Sciences, Cluj-Napoca, Romania; ghermanclaudia@yahoo.com*
[4]*Emergency County Hospital, Second Surgical Clinic, Department of Vascular Surgery, Cluj-Napoca, Romania*

Abstract

Peripheral arterial disease (PAD) directly affects the quality of life, patients experimenting limited walking ability and disability. The purpose of the current study was to investigate the walking and climbing patterns of patients with lower extremity PAD in relation with several risk factors, applied on Romanian population. A cohort non-randomized design was conducted and all eligible subjects who self-referred for medical care since March 2016 until February 2017 at the Second Surgery Department, County Clinical Emergency Hospital of Cluj-Napoca were included. The eligible patients were older than 18 years, with leg pain and Rutherford grade from I to IV. The following tests were applied to each subject included in the study to investigate the capacity to walk as far as possible in six minute (6 minute walking test), the capacity to climb stairs (climbing stairs test) and the capacity to walk on a treadmill (treadmill test) until the pain occurred. Twenty-four patients with mean age of 65.08±8.53 years were investigated. Almost 81% of patients were with chronic pain, 46% were overweight, and 79% were smokers. The results on applied walking tests were as follows: 279.17±70.58 meters to 6-minutes walking test, 77.50±21.80 stairs and 182.50±73.34 meters on treadmill test. The results of the walking tests significantly correlate with each other ($\rho>0.93$, $p<0.0001$), and all applied tests significantly correlate with toe gangrene ($\rho>|0.52|$, $p<0.01$) and toe disarticulation ($\rho>0.62$, $p<0.002$). It can be concluded that any of the applied walking test proved reliable instrument, able to identify the patients with most severe PAD.

Keywords: claudication, peripheral arterial diseases, reliable tool, walking tests

Introduction

Atherosclerosis affects up to 10% of the Western population older than 65 years (Selvin and Erlinger, 2004). Peripheral artery disease is an obstructive disease caused by the process of atherosclerosis, characterized by a narrowing of the peripheral vessels like legs arteries, mesenteric arteries, brain arteries, but most commonly in the arteries of the legs, PAD being highly similar to coronary artery disease (Gerhard-Herman *et al*., 2016). Predicted mortality for PAD patients with claudication is approximately 30% at 5 years, 50% at 10 years, and 70% at 15 years (Norgren *et al*., 2007).

As symptoms, claudication occurs during physical activity and is relieved after a short rest later pain develops because of inadequate blood flow. Under resting conditions, normal blood flow to extremity muscle groups averages 300-400 mL/min. Once the exercise begins, blood flow increases as much as 10-fold as a consequence of the increase in cardiac output and compensatory vasodilation at the tissue level. This allows the increase in oxygen demand to be met. When exercise ceases, blood flow returns to normal within minutes (Dominguez, 2017).

Surgical treatment options, are typically reserved for patients with more severe disease or those in whom non-surgical management (vasodilators, platelet antiaggregants or prostaglandin treatments) fails, including: bypass surgery and endovascular therapy (e.g. stents, balloons, or atherectomy devices). Whereas open surgery dominated the treatment options two decades ago, endovascular

Received: 29 Sep 2017. Received in revised form: 14 Nov 2017. Accepted: 16 Nov 2017. Published online: 20 Dec 2017.

management of PAD has become exponentially more popular since then (Rowe *et al*., 2009). Overall, recommendations for selecting a treatment modality may depend on the patient's life expectancy and comorbid conditions, as well as on the extent of the occlusive disease (Antoniou *et al*., 2013).

Three tests, named 6-minute walking test, climbing stairs test, treadmill test, were used in the evaluation. These tests have been initially developed to assess the physical fitness in healthy subjects (Balke, 1963) and then applied to test the exercise tolerance in chronic respiratory disease and heart failure (ATS 2002; Guyatt *et al*., 1985). The 6-minute walking test (6MWT) has highly reliable measurements, which are in direct correlation with the functional and hemodynamic severity of PAD (Montgomery and Gardner, 1988). The treadmill test allows to accurately estimate walking distances (Saskia *et al*., 2010), while the climbing stairs test reveals the severe cases of PAD (Atul Jain *et al*., 2012).

The selected tests for the current study exhibit good test-retest reliability, whereas other walking tests such as timed up and go, sit and stand test, 4 m gait speed test, lack conclusive data to support their practical use. In the last 10 years there has been a growing interest among medical practitioners towards the walking tests and the body of evidence regarding these tests' practical relevance is on the ascending path. For example, lower results during one of the walking tests is strongly correlated with longer hospitalization and mortality in people with chronic respiratory disease (Holland *et al*., 2014), but there is further necessity for studies to evaluate their relevance and utility in PAD.

The purpose of our study was to investigate the walking pattern of patients with lower extremity PAD in relation with body mass index, metabolic and cardiovascular co-morbidities and smoking status as risk factors in a Romanian cohort.

Materials and Methods

The overall evaluation was an observational study conducted between March 2016 and February 2017 on convenient sample of subjects hospitalized at the Second Surgery Clinic, Emergency County Hospital in Cluj-Napoca, Romania.

Patients with Rutherford grade between I (mild claudication) and IV (ischemic rest pain with ulceration and gangrene) were included in the study according to the following criteria: ankle pressure (ABI = ankle-brachial index) < 0.9, age > 18 years old and leg pain. These were eligible for participation in the study, and were included in the study depending on the time-frame granted for the data collection before treatment. Patients with absence of PAD (ABI > 0.90), inability to obtain an ABI measure, asymptomatic PAD (Rutherford grade 0), exercise tolerance limited by other factors than leg pain (dyspnea, active cancer, renal disease, liver disease, coronary disease) were excluded from the study.

The inclusion and exclusion criteria applied in this study are presented in Fig. 1.

For this cohort, the following data were recorded: the demographic characteristics (gender, age, living area (rural/urban) and education), risk factors (body mass index, smoking status, and co-morbidities such as type II diabetes, arterial hypertension, ischemic heart disease, other cardiac diseases and stroke if exists), signs and symptoms of peripheral arterial disease (continuous pain, toe gangrene etc.), and surgical interventions (toe disarticulation, necrectomy etc.). The flowchart of the applied design is presented in Fig. 2.

Three different walking tests were applied to each subject included in the cohort: 6-minute walking test (record the individual capacity to walk as far as possible in six minute), climbing stairs test (record the individual capacity to climb a number of stairs untill the pain occurs), and treadmill test (record the individual capacity to walk on a treadmill until the pain is felt).

The 6-minute walking test is conducted by placing two poles at a distance of 30 m between them, whereas a full lap is considered a round of 60 walk. Then it is recorded how many laps each patient can undergo and the participant can stop to rest if needed (this data is also recorded).

Treadmill walking test is conducted as follows: the test begins with the treadmill set to a low speed (1 km per hour) at 10% incline, and every 3 minutes the speed is increased by 0.5 km/hour. The test continues for a maximum of 30 minutes (usually attainable only by well-trained individuals) or until the patient quits or develops signs or symptoms of ischemia or an arrhythmia.

For climbing stairs test, the time (in seconds) taken to ascend and descend a flight of stairs (2-6) is recorded. The number of stairs will depend on individual environmental situations. Suitable steps are considered to be between 16-20 cm high, while the used ones were 18 cm. The patient is asked to ascend and descend a flight of stairs as quickly as possible but in a safe manner. The participant can stop and

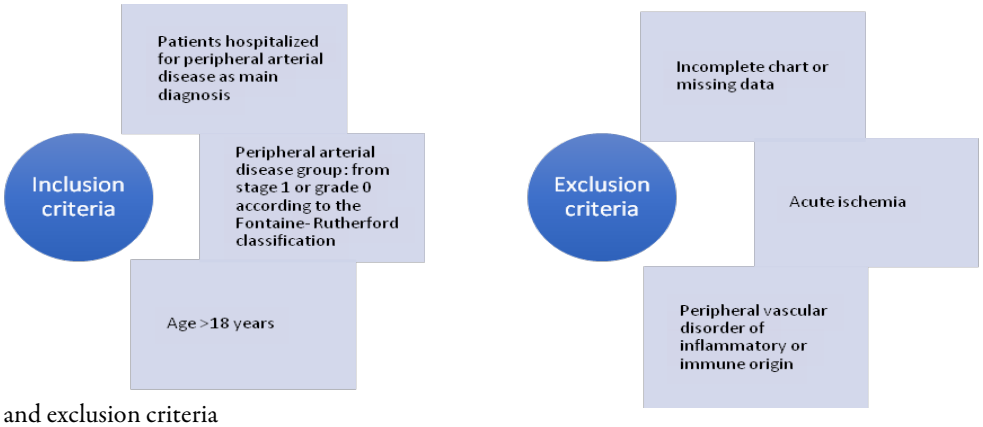

Fig. 1. Inclusion and exclusion criteria

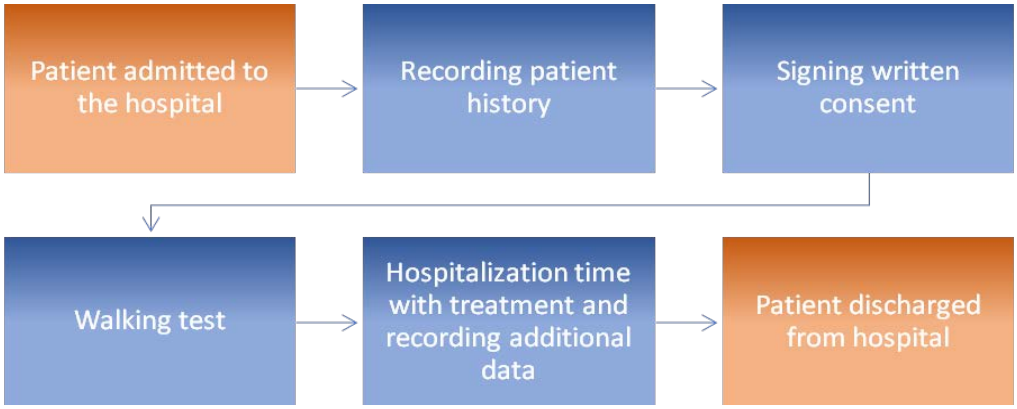

Fig. 2. Study design flowchart

rest if needed, but the time keeps going. Using a handrail and walking aid is also permitted if needed, but this should be recorded. Timing begins on the signal to start and terminates when the participant returns with both feet to the ground level.

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethical Committee of our university (no. 66/14.03.2016). All patients agreed to participate and signed an informed written consent.

The data were analyzed according with to type and distribution. The frequencies as absolute and percentage were reported for qualitative data. Shapiro-Wilk test was used to test the normal distribution of quantitative data. Quantitative data were summarized as arithmetic mean and standard deviation for normally distributed data; otherwise median and interquartile range (defined as (Q1-Q3) where Q1 = 25th percentile and Q3 = 75th percentile) were used. Z test with continuity correction (Zc) was used to test the significance of marginal proportions:

Zc-statistic = [(p-p0)+c]/sqrt(p0*(1-p0)/n,

where 'p' and 'p0' are the proportions to compare, 'c' is the correction factor and is -1/(2*n) if p>p0, 1/(2*n) if p<p0, and 0 if |p-p0|<1/(2*n)).

The association between the results of different applied walking tests was tested with Spearman rank correlation coefficient (ρ). Statistical analysis was conducted with Statistica program (v. 8, StatSoft) at a significance level of 5%.

Table 1. Demographic characteristics of the investigated cohort

Variable	Value
Age, years (mean ± stdev)	65.08±8.53
Gender (no. (%))	
Men	22 (91.67)
Women	2 (5.88)
Environment, rural (no. (%))	12 (50.00)
Education	
Medium studies	12 (50.00)
Intellectuals	12 (50.00)
BMI, kg/m^2 (mean±stdev)	25.40±4.03

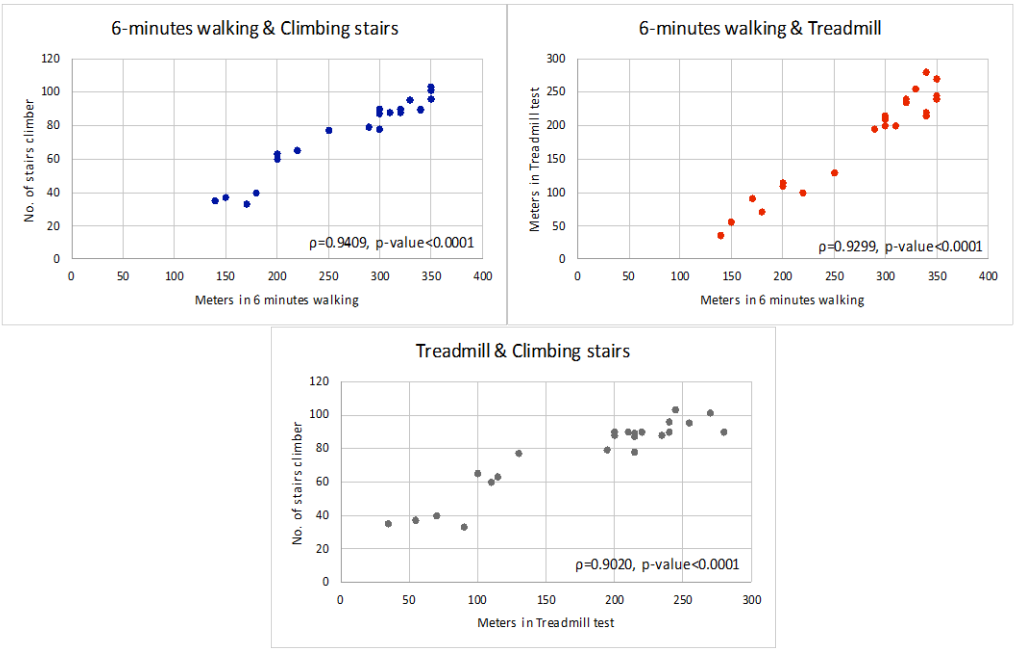

Fig. 3. Relations between pairs of applied walking tests on PAD patients

Table 2. Co-morbidities within the investigated cohort

Co-morbidity	No. (%)	Z-stat (p-value)
Type II diabetes, yes	15 (62.50)	-2.53 (0.0114)
Blood hypertension, yes	18 (75.00)	-5.66 (< 0.0001)
Ischemic heart disease, yes	13 (54.17)	-0.82 (0.4122)
Cardiac rhythm disorders, yes	4 (6.67)	8.76 (< 0.0001)

Table 3. Descriptive results of applied tests

Test	Minimum	Maximum	Mean ± StDev	Median (Q1-Q3)
6-minutes walking, meters	140	350	279.17±70.58	300 (215.00–340.00)
Climbing stairs, stairs	33	103	77.50±21.80	88 (64.50–90.00)
Treadmill, meters	35	280	182.50±73.34	212.5 (113.75–240.00)
Treadmill, minutes	3	12	9.63±2.70	11 (8.00–12.00)

StDev=standard deviation; Q1 = 25th percentile; Q3 = 75th percentile

Table 4. The minimum values for investigated walking tests by groups

Sub-group	6-minutes walking test (m)	Climbing stairs test (no. of stairs)	Treadmill test (min)
toe disarticulation (n = 3)	170	33	8
toe gangrene (n = 4)	140	35	3

Results

A cohort of twenty-four patients aged between 48 and 81 years have been included in the study. As expected, due to the characteristics of the disease, a significant higher percentage were men (Zc-statistic = -14.40, p-value<0.0001). Half of the patients were overweight (11 patients) or obese (one patient). Demographic characteristics of the cohort are presented in Table 1.

The duration of the disease varied from 1 to 156 weeks with a median of 23 weeks and an interquartile range of (2.75-42.00).

Most of the patients were with continuous pain at the inclusion in the study (17 (78.83%), Z-statistic = -4.49, p-value<0.0001). Most of the patients included in the study were smokers (19 (79.17%), Z-statistic = -7.04, p-value<0.0001).

Excepting ischemic heart disease, all other investigated co-morbidities were significant from statistical point of view (Table 2). Three patients (12.50%) were with gangrene and four had a by-pass (16.67%).

The summary of the applied tests is presented in Table 3. Significant association has been observed between applied walking tests (Fig. 3).

All applied walking tests correlated significantly with toe gangrene (ρ<0.52|, p-value<0.01) and toe disarticulation (ρ<0.62, p-value<0.002), cases in which the values were lower as compared with performances when gangrene or disarticulation is not present (Table 4).

Discussion

The assessment of patients with PAD using three walking tests was successfully conducted. The patient's mean age was 65 years, result similar to that reported by Criqui and Aboyans (2015) in their study where it was highlighted that PAD is uncommon in patients with age before 50 years and have a pick at 80 years.

It is well known that PAD occurs more frequent in men compared with women, demonstrated also by the hereby results (see Table 1). Although this gap inclines to decrease and to even the proportions, there are still regions, like Romania disparity between sexes (Malik *et al*., 2004; The PARTNERS program, 2001).

The current study revealed a 50-50% distribution regarding environment and education level. In specialty literature predominates the rural environment and medium level of education of the patients (Shammas, 2007). The obtained result is similar to the one reported in the scientific literature (Ciocan *et al*., 2017).

Half of the patients in the studied cohort were at the border between normal weight and overweight (Table 1). It is known that obesity is frequently observed among subjects with PAD in association with atherosclerosis (Gorter *et al*., 2004; NCEP Expert Panel, 2001).

The study revealed that the median period of time from the first severe symptoms to the hospital presentation ranged between 1 to 156 weeks, a quarter of patients presented to the hospital after 42 weeks. No studies that measured this time frame were found in the available scientific literature. This period influences the stage of disease at admission, more severe symptoms making the patient seek professional help earlier (McDermott *et al*., 2001; Conte *et al*., 2015; Ratchford, 2017).

As expected, smoking is directly linked with PAD, most of the patients in the cohort being smokers (p<0.0001). PAD patients are smokers, the frequency identified in our study being similar with the one reported by other studies (Anderson *et al*., 2001; Conen *et al*., 2011). It is known that smoking affects arteries and speeds the development of atherosclerosis (Cui *et al*., 2006), leading also to a fast decrease in the quality of life (Fritschi *et al*., 2013).

Diabetes, arterial hypertension and cardiac rhythm disorders were co-morbidities observed in our cohort (Table 2). Blood hypertension and type II diabetes were present to the majority of the investigated patients, while on the opposite, the cardiac rhythm disorders were less frequent observed. Diabetes is known as the strongest predictor of PAD and the association of these two diseases leads to amputation faster (Athyros *et al*., 2004; Cerqueira *et al*., 2008; Shammas, 2007). Selvin shows in the National Health and Nutrition Survey (NHANES) that arterial hypertension is strongly correlated with PAD (Selvin and Erlinger, 2004). Rhythm disorders decrease the patient's biologic balance and affect the quality of life (Feringa *et al*., 2006; Qureshi *et al*., 2015).

Half of the patients in the cohort succeeded to walk 300 meters to the 6 minutes walking test, results similar with other studies reported in the scientific literature. In Tsai's study and other studies, the mean of meters walk in 6 minutes walking test was equal with 350 meters (Tsai *et al*., 2002; Beatty *et al*., 2012; Nash, 2012).

Regarding the climbing test, the current study revealed a median of 88 stairs, showing that half of patients included in the study succeeded to climb 88 stairs. As the subjects are evaluated on stairs of 16-20 cm height, the results are expected to be equivalent. There were not identified in the available literature, any studies that evaluated the number of stairs climbed by patients with PAD.

The results related with treadmill test show that, patients need to stop after 11 minutes, and the median distance walked was equal to 212.5 meters (Table 3). In Hiatt's study, also confirmed by other studies, is revealed that if a patient walks on a Treadmill 3 hour per week during 12 weeks, his/her performance improves within 24 months and the improvements are even higher compared to the strength training (3 hours/week of resistive training of five muscle groups of each leg) (Hiatt *et al*., 1994; Libby *et al*., 2007; Regensteiner *et al*., 2002). This underlines the importance of exercises in the evolution of PAD and that a sedentary life style will badly influence the natural course of the disease (Craft *et al*., 2008; Acampa *et al*., 2016; Gibbons *et al*., 2002).

The performances in the applied tests decrease, as expected, in the presence of toe gangrene or disarticulation (Table 4) with significant correlation between walking performances and toe gangrene or disarticulation ($p<0.002$). Major events occurring in the natural evolution of the disease, like toe gangrene and toe disarticulation affects the ability of walking, translating in a poor result during tests, conclusion supported by other researchers (Ciocan *et al*., 2015).

As expected, a positive, very good association, statistically significant was observed between pairs of applied walking tests (Fig. 1). The highest association was observed between 6 minutes walking test and climbing stairs test (correlation equal with 0.94). This result showed that, from a clinically point of view, any of these investigated tests are good in the evaluation of patients with PAD. The efficiency of 6 minutes walking test and Treadmill test had also been demonstrated on patients with cardiac diseases (Enright, 2003; Wise and Brown, 2009).

The investigated walking and climbing tests are not investigated enough in lower limb arterial diseases. Studying this may provide an important glimpse in the physical examination of arterial patients at admission and extended also after any medical strategy, either surgical or non-surgical, in order to evaluate its efficiency. Not only is it a reliable instrument to objectively assess the PAD patients' capacity to use their limbs and determine to what extend PAD has affected them, but they are also an extremely cheap and fast tool. Walking tests can further be used to evaluate one's response to treatment, therefore enabling the physician to choose the best suited treatment strategy for each individual, with the best functional result respectively.

The current study is a pilot study and developing this area is essential for further results regarding walking tests.

Conclusions

Testing patients with lower extremity peripheral artery using walking and climbing tests brings an objective measure on the functional capacity of the patients of using their affected patients' lower limbs. The obtained results show that half of the investigated patients with PAD were able to walk 300 steps in 6 minutes, 212 steps in 11 minutes according to treadmill test and were able to climb 88 stairs until the pain imposed resting. The performances in these tests decreased in the presence of toe gangrene or disarticulation. Any of the applied walking tests proved equally reliable instruments able to identify the patients with most severe PAD.

Acknowledgements

The research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

Acampa W, Assante R, Zampella E (2016). The role of treadmill exercise testing in women. Journal Nuclear Cardiology 23(5):991-996.

Anderson JE, Jorenby DE, Scott WJ, Fiore MC (2002). Treating Tobacco Use and Dependence. Chest 121(3):932-941.

Antoniou GA, Chalmers N, Georgiadis GS, Lazarides MK, Antoniou SA, Serracino-Inglott F, Smyth JV, Murray D (2013). A meta-analysis of endovascular versus surgical reconstruction of femoropopliteal arterial disease. Journal of Vascular Surgery 57(1):242-253.

Athyros VG, Mikhailidis DP, Papageorgiou AA, Ganotakis TES, Symeonidis AN (2004). METS-GREECE Collaborative Group Prevalence of atherosclerotic vascular disease among subjects with the metabolic syndrome with or without diabetes mellitus: the METS-GREECE Multicentre Study. Current Medical Research and Opinion 20:1691-1701.

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories (2002). ATS statement: guidelines for the six-minute walk test. American Journal of Respiratory and Critical Care Medicine 166:111-117.

Balke B (1963). A simple field test for the assessment of physical fitness. Civile Aeromedical Research Institute US 53:1-8.

Beatty AL, Schiller NB, Whooley MA (2012). Six-minute walk test as a prognostic tool in stable coronary heart disease: Data from the Heart and Soul Study. Archives of Internal Medicine 172(14):1096-1102.

Cerqueira MD, Nguyen P, Staehr P, Underwood SR, Iskandrian AE (2008). Effects of age, gender, obesity, and diabetes on the efficacy and safety of the selective A2A agonist regadenoson versus adenosine in myocardial perfusion imaging integrated ADVANCE-MPI trial results. JACC Cardiovascular Imaging 1(3):307-316.

Ciocan RA, Bolboacă SD, Drugan T, Rădulescu S, Gherman CD (2015). Clinical Management and Risk of Amputation among Patients with Critical Lower Limb Ischemia. In: Dumitrascu DL, Portincasa P (Eds). Proceedings of the 49th Annual Scientific Meeting of the European Society for Clinical Investigation pp 113-118.

Ciocan RA, Bolboaca SD, Radulescu S, Stancu B, Ciocan A, Gherman CD (2017). Demographic and comorbidity pattern of patients with citical limb ischemia. Folia Medica 59(1):14-22.

Conen D, Everett BM, Kurth T, Creager MA, Buring JE,Ridker PM, Pradhan AD (2011). Smoking, smoking status and risk for symptomatic peripheral artery disease in women: a cohort study. Annals of Internal Medicine 154(11):719-726.

Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JF, Clair DC, Geraghty PJ, McKinsey JF, Mills JL, Moneta GL (2015). Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. Journal of Vascular Surgery 61(3 Suppl):2S-41S.

Craft LL, Guralnik JM, Ferrucci L, Liu K, McDermott MM (2008). Physical activity during daily life and circulating biomarker levels in patients with peripheral arterial disease. American Journal of Cardiology 102(9):1263-1268.

Criqui MH, Aboyans V (2015). Epidemiology of Peripheral Artery Disease. Circulation Research 116:1509-1526.

Cui R, Iso H, Yamagishi K, Tanigawa T, Imano H, Shimamoto T (2006). Relationship of smoking and smoking cessation with ankle-to-arm blood pressure index in elderly Japanese men. European Journal of Cardiovascular Preventive Rehabilitation 13(2):243-248.

Dominguez JA, Rowe VL (2017). Peripheral arterial occlusive disease clinical presentation. The heart organization. Medscape. http://emedicine.medscape.com/article/460178-clinical.

Enright PL (2003). The six-minute walk test. Respiratory Care 48(8):783-785.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2001). Journal of the American Medical Association 285:2486-2497.

Feringa HH, Van Waning VH, Bax JJ, Elhendy A, Poldermans D (2006). Cardioprotective medication is associated with improved survival in patients with peripheral arterial disease. Journal of the American College of Cardiology 47:1182-1187.

Fritschi C, Collins EG, O'Connell S, McBurney C, Butler J, Edwards L (2013). The effects of smoking status on walking ability and health-related quality-of-life in patients with peripheral arterial disease. The Journal of Cardiovascular Nursing 28(4):380-386.

Gerhard-Herman MD, Gornik HL, Barett C (2016). 2016 AHA/ACC Guideline on the management of patients with lower extremity peripheral artery disease. Circulation 136(13):11.

Gibbons RJ, Balady GJ, Bricker JT (2002). ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Journal of American College of Cardiology 40(8):1531-1540.

Gorter PM, Olijhoek JK, van der Graaf Y (2004). SMART Study Group Prevalence of the metabolic syndrome in patients with coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm. Atherosclerosis 173:363-369.

Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, Berman LB (1985). The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Canadian Medical Association Journal 132:919-923.

Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG (1994). Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease. Implications for the mechanism of the training response. Circulation 90:1866-1874.

Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Hiatt WR (2001). Peripheral arterial disease detection, awareness, and treatment in primary care. Journal of the American Medical Association. 286(11):1317-1324.

Holland AE, Spruit MA, Troosters T, Puhan MA (2014). An official European Respiratory Society/ American Thoracic Society technical standard: field walking tests in chronic respiratory disease. European Respiratory Journal 44(6):1428-1446.

Jain A, Liu K, Ferrucci L, Criqui MH, Tian L, Guralnik JM, Tao H, McDermott MM (2012). The walking impairment questionnaire stair-climbing score predicts mortality in men and women with peripheral arterial disease. Journal of Vascular Surgery 55(6):1662-1673.e2.

Libby P, Bonow RO, Mann DL, Zipes DP (2007). Exercise stress testing. In: Braunwald E (Ed). Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 8th ed. Philadelphia, Pa: WB Saunders.

Malik S, Wong ND, Franklin SS (2004). Impact of the metabolic syndrome on the mortality from coronary heart disease, cardiovascular disease and all causes in United States of America. Circulation 110:1245-1250.

McDermott MM, Greenland P, Liu K, Martin GJ (2001). Leg symptoms commonly reported by men and women with lower extremity peripheral arterial disease: Associated clinical characteristics and functional impairment. Journal of the American Medical Association 286(13):1599-1606.

Montgomery PS, Gardner AW (1988). The clinical utility of a six-minute walk test in peripheral arterial oclusive disease patients. Journal of American Geriatry Society 46(6):706-711.

Nash DT (2012). Time for a 6-minute walk? Archives of Internal Medicine 172(14):1102-1103.

Nicolai SP, Leffers P, Kruidenier LM, De Bie RA, Prins MH, Teijink JA (2010). Extending the Range of treadmill testing for patients with intermittent claudication. Medicine & Science in Sports & Exercise 42(4):640-645.

Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, *et al.* (2007). Inter-society consensus for the management of peripheral arterial disease (TASC II). Journal of Vascular Surgery 45(1): S5-67.

Qureshi WT, Alirhayim Z, Blaha MJ, Al-Mallah MH (2015). Cardiorespiratory fitness and risk of incident atrial fibrillation: results from the Henry Ford exercise testing (FIT) Project. Circulation 131(21):1827-1834.

Ratchford EV (2017). Medical management of claudication. Journal of Vascular Surgery 66(1):275-280.

Regensteiner JG, Ware JE Jr, McCarthy WJ, Zhang P, Forbes WP, Heckman, Hiatt WR (2002). Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. Journal of American Geriatry Society 50:1939-1946.

Rowe VL, Lee W, Weaver FA, Etzioni D (2009). Patterns of treatment for peripheral arterial disease in the United States: 1996-2005. Journal of Vascular Surgery 49(4):910-917.

Selvin E, Erlinger TP (2004). Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation 110(6):738-743.

Shammas NW (2007). Epidemiology, classification, and modifiable risk factors of peripheral arterial disease. Vascular Health and Risk Management 3(2):229-234.

Tsai JC, Chan P, Wang CH, Jeng C, Hsieh MH, Kao PF, Chen YJ, Liu JC (2002). The effects of exercise training on walking function and perception of health status in elderly patients with peripheral arterial occlusive disease. Journal of Internal Medicine 252:448-455.

Wise RA, Brown CD (2005). Minimal clinically Important Differences in the Six-Minute Walk Test and the Incremental Shuttle Walking Test. COPD: Journal of Chronic Obstructive Pulmonary Disease 2(1):125-129.