

**Clinical validation of the *Walking Impairment Questionnaire* in patients
with peripheral arterial disease: defining high and low walking
performance values**

by

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A thesis submitted to the Department of Community Health and Epidemiology

In conformity with the requirements for

the degree of Master of Science

Queen's University

Kingston, Ontario, Canada

(August 2011)

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Abstract

Objective: The validity of the *Walking Impairment Questionnaire* (WIQ) as a clinical tool for use by clinicians in the conservative management of patients with peripheral arterial disease (PAD) has not been well established. The objective of this study was to determine the validity of the WIQ as a tool to identify high and low walking ability (performance) in patients with PAD.

Methods: We conducted a cross-sectional study and enrolled 132 new and existing PAD patients who consecutively attended the vascular clinic at Kingston General Hospital between May 2010 and May 2011. Patients with an Ankle Brachial Index ≤ 0.9 were approached for study inclusion. Participants were excluded if they had (a) severe ischemia requiring intervention; (b) comorbid conditions that limited walking (angina, congestive heart failure, chronic obstructive pulmonary disease or severe arthritis); (c) wheel chair, cane or walker requirement; (d) non-compressible arteries; and/or (e) severe cognitive impairment. Walking performance was assessed with the *Walking Impairment Questionnaire* (surrogate measure) and a standardized graded treadmill test (gold standard measure). Other study variables were obtained via questionnaire (age, sex, comorbid conditions and smoking status) or direct measurement (weight, height, waist circumference).

Results: 123 patients completed the treadmill test (70.7% males, mean age of 66.5 and mean ABI of 0.6 with range 0-0.9). The scores on the WIQ ranged from 0 to 100 and absolute claudication distance (ACD) ranged from 0.03 to 0.98 miles. All WIQ subscale and overall scores were positively and moderately associated with the ACD (r values 0.63

to 0.68, $p < 0.05$). Based on the area under the curve of the receiver operating characteristics curve analysis, an overall WIQ score of 42.5 or less identified low performers (sensitivity 0.9, specificity 0.7, area under the curve 0.89) while a combined distance and stair score of 75.5 or more identified high performers (sensitivity 0.4, specificity 0.9, area under the curve 0.81).

Conclusions: Based on these findings, the WIQ, an easily administered self-report questionnaire, and the cutoffs identified could be used to quantify and classify walking ability in PAD patients, making this a potentially useful tool for clinicians to manage PAD patients.

Co-Authorship

This thesis is the original work of Stephen Sagar under the supervision of Drs. Joan Tranmer (primary supervisor), Peter Brown and William Pickett. The research objectives, design, analysis, and interpretation of findings were the sole work of Stephen Sagar with input from Drs. Tranmer and Pickett. Writing of the manuscript and writing of thesis chapters was performed by Stephen Sagar with supervision by Drs. Tranmer and editorial feedback from Drs. Brown and Pickett.

Acknowledgements

I would like to acknowledge the hard work and guidance of my supervisors, Drs. Joan Tranmer (Primary), Peter Brown and William Pickett. Your constructive feedback and positive attitude have helped me learn and develop both as a scientist and an individual. Your focus on personal health, personal development and work/family balance is something to which I aspire.

I would like to thank the faculty, staff and students of the department of Community Health and Epidemiology for providing a positive learning environment. I would like to acknowledge my lab-mates. Thank you for acting as a sounding board for my sometimes ridiculous ideas and for providing a constant source of entertainment and lifting my spirit when I was down. Thank you and best wishes for your future work to Lynda Reid for your tremendous help with patient testing and data entry.

I would like to acknowledge Queen's University for providing me with an intellectually stimulating environment over the past six years. I would also like to thank QFA, QSC, Camp Outlook, the Queen's cycling and triathlon teams and Beat'em and Treat'em for helping me grow and develop as an individual. I believe the skills and lessons I learnt through these extracurricular activities have prepared me to face, and possibly thrive in, the world outside the Queen's bubble.

On a technical note, I would like to thank the Sagarsaurus Rex, the Veloci-Sagar, two of my bikes, for providing motivation to get through my days work and keeping me physically active. Thanks also to my commuter bikes for ensuring I made it to work day-

in and day-out through rain, wind and snow. I would also like to acknowledge the internet for allowing me to stream television shows and not waste time on commercials.

Finally I would like to extend a special thanks to my friends and family (I will thank each of you in person) for your continued encouragement and your ability to make me laugh. To my parents: thank you for your support throughout my education and for helping me believe I could accomplish anything. You have helped make me the person I am today and for that I am truly thankful (although you can ease up on the puns).

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List of Acronyms

ABI: ankle-brachial index

ACD: absolute claudication distance

FCD: functional claudication distance

ICD: initial claudication distance

OR: odds ratio

PAD: peripheral arterial disease

ROC: receiver operating characteristics

WIQ: *Walking Impairment Questionnaire*

Chapter 1

General Introduction

1.1 Background and rationale

Peripheral arterial disease (PAD) is a prevalent chronic condition that increases with age, affecting 20% of patients over the age of 75 years. PAD is associated with an exceptionally high risk of cardiac and cerebrovascular events (1,2). Intermittent claudication, defined as the onset of pain in the leg or gluteal muscles with exertion which resolves with a few minutes of rest (1,2), is a sentinel symptom of PAD and, in most cases, indicative of disease severity. The prevalence and effects of claudication on walking performance vary within this population even for patients with similar clinical profiles. Given that the primary goal of conservative clinical management of PAD is to minimize disease progression and optimize performance, it is important clinically to be able to easily assess performance and the effects of treatment, including lifestyle modification, on walking performance. Walking performance has been assessed objectively via self-report tools or standardized treadmill tests (3-13). Many clinicians may not use standardized measures and rely solely on patient's subjective responses to their questioning (personal communication, 2010, Zelt and Brown). Thus it is difficult to quantify, monitor and accurately assess patients' levels of performance across the continuum of this chronic condition.

Single stage and graded treadmill tests have been used to determine onset of pain and maximum distance walked as measurements of a patient's walking ability (4). While

these tests may provide insight into the severity of claudication they are not often feasible in a clinical setting. The *Walking Impairment Questionnaire* (WIQ) (14), a fourteen item tool, has been used in a limited number of research studies (9). Previous studies that have focussed on the WIQ and treadmill testing are limited by small sample sizes (e.g.: 26 patients (11)) and to the study of patients with intermittent claudication (10-12,15). Thus these studies may not have thoroughly addressed the diverse nature of the PAD population and the wide range of observed symptoms (9,12). Results of these studies may therefore not be generalizable to the larger PAD population. The only study to investigate the validity of the WIQ in a diverse population did so by comparing the results to the 4-metre walking velocity (16,17) and 6-minute walking score (17), not a graded treadmill test (9). We have the opportunity to address this gap in the clinical research literature.

1.2 Objectives and relevance

The overall goal of this research was to determine the validity of the *Walking Impairment Questionnaire* as a tool to identify high and low levels of walking ability in patients with PAD. Our specific objectives were:

- (A) To determine the criterion validity of the WIQ;
- (B) To determine cut-off scores for the WIQ to identify patients with low or high walking ability;
- (C) To provide suggestions for ongoing clinical use of the WIQ.

Validation of the WIQ would provide clinicians with an assessment tool that could be routinely completed by the patient at each clinic visit in order to monitor impact of claudication pain on walking performance. The WIQ has previously been validated as a tool to determine changes in walking performance following treatment (10), but its validity as an assessment/management tool has not been determined. Information obtained from the WIQ in combination with knowledge of patients' clinical conditions and risk factors would assist with clinicians' management and monitoring of patients' symptoms. Validation of the WIQ against the treadmill test would also permit its use in epidemiological studies, to allow for further investigation of experiences with PAD.

1.3 Study design

We conducted a cross-sectional study of consecutive PAD patients from the vascular clinic at Kingston General Hospital between May 2010 and May 2011. All patients (new and existing) who met the clinical inclusion criteria were approached for study inclusion. Walking performance was assessed with the *Walking Impairment Questionnaire* (surrogate measure) and a standardized graded treadmill test (18) (gold standard measure). Other variables were obtained via self-report questionnaire (age, sex, comorbid conditions and smoking status) or direct measurement (weight, height, waist circumference).

1.4 Thesis organization

This thesis conforms to the regulations outlined by the Queen's University School of Graduate Studies. The second chapter summarizes studies of relevance to the focus of

this study: the WIQ and its validity as an evaluation tool to measure walking ability. The third chapter describes the research methods employed in this thesis. The fourth chapter is a manuscript entitled: *Determination of valid cut-off points for use of the Walking Impairment Questionnaire for the identification of walking ability in patients with peripheral arterial disease* to be submitted for publication to the Journal of Vascular Surgery. The fifth chapter presents additional results; results not presented in the manuscript. The final chapter of the thesis consists of a general discussion of findings, as well as overall conclusions and suggestions for future research directions.

1.5 Student Contributions

As a research assistant on the PAD project, the candidate participated in patient screening, questionnaire compilation, protocol design, database design, data entry and participant testing. Under the supervision of Drs. Tranmer, Brown and Pickett, the candidate performed all data analyses and led the writing of all chapters of this thesis including the manuscript. The candidate also participated in the dissemination of the results through oral presentations at both the *Fourteenth Annual Scientific Meeting for Health Science Research Trainees* in the Faculty of Health Science at Queen's University and the *2011 Canadian Society of Epidemiology and Biostatistics National Student Conference*.

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Chapter 2

Literature Review

2.1 Key terms and definitions

Peripheral arterial disease (PAD) is one of the most important localizations of atherosclerosis after coronary heart disease and cerebrovascular disease (1). Growth of atherosclerotic plaque leads to stenosis and occlusions of arteries in the lower extremities resulting in symptomatic manifestations of the disease (1-3).

The *ankle brachial index* (ABI) is a simple tool for objectively measuring quality of circulation in the lower extremities (4). It is measured by dividing the ankle systolic blood pressure (highest of the posterior tibial and dorsalis pedis pulses for each leg) by the highest brachial systolic blood pressure (4). A lower ABI indicates more severe PAD, compromised circulation and stenosis (5).

Intermittent claudication is a primary symptom of PAD, and is defined as the onset of pain in the leg or gluteal muscles with exertion which resolves with a few minutes of rest (6,7).

2.2 PAD

2.2.1 Prevalence

Peripheral arterial disease of the lower extremities is a prevalent chronic condition that increases with age, and is associated with exceptionally high risks for cardiac and cerebrovascular events (7). Findings from a recent USA epidemiological study suggest that approximately 5 million American adults suffer from PAD, based on a prevalence of 4.3% (95% CI 3.1% to 5.5%) for individuals over 40 years and a prevalence of 14.5% (95% CI 10.8% to 18.2%) for individuals over 70 years (8). There is an absence of Canadian data surrounding the prevalence of PAD; however, some have estimated the prevalence to be approximately 4% of the population aged 40 years and older (9).

2.2.2 Diagnosis and assessment

The severity of PAD is assessed clinically according to the level of arterial occlusion. The ankle brachial index (ABI) is a common non-invasive assessment of the degree of occlusion (2,5). The disease can be classified into three categories based on the ABI: mild (0.7 to 0.9), moderate (0.5 to 0.69), and severe (less than 0.5) (7). Further diagnostic assessment of patients also includes ultrasonic duplex scanning to identify presence of atherosclerotic plaque, areas of calcification, and the level of the occlusion, but it does not provide an accurate measurement of the degree of occlusion (10). Computed tomographic angiography and magnetic resonance angiography are two methods that detect more precisely the severity of the occlusion. Contrast angiography is

another invasive method of evaluation of the occlusion. All three types of angiography are associated with some risk to the patient due to the nature of the tests. Their use may therefore be reserved for severe cases and those for whom revascularization is planned.

2.2.3 Clinical presentation, prognosis and natural history

Patients can be classified based on the severity of disease as measured by the ABI. However, a low ABI score, normally associated with more severe intermittent claudication (11), does not always correspond to the severity of symptoms, such as low walking performance or more claudication pain (7). PAD patients can also be classified based on the severity of their symptoms.

Intermittent claudication is the onset of pain in the leg or gluteal muscles with exertion that resolves within a few minutes of rest (6,7). Approximately 20-50% of PAD patients present initially with no symptoms, 40-50% present with atypical leg pain, 10-35% with intermittent claudication and 1-2% with chronic leg ischemia (10,12). 50% of patients with intermittent claudication show either no change in symptoms or improvement in function after 5 years (10,12). After 5 years, symptoms progress in 16% of patients with intermittent claudication (10,12). Furthermore, 25% of patients with intermittent claudication will require surgery or experience tissue loss within 5 years of diagnosis, yet less than 4% of these patients require amputation (10,12). The 5-year mortality rate is 15-30%, of which 75% is due to cardiovascular causes (10,12). Another 20% of patients with intermittent claudication will experience a non-fatal cardiovascular event (10,12). After 1 year, 25% of patients with critical limb ischemia require

amputation, and mortality due to cardiovascular causes is 25% in these patients (10,12). It is important to treat patients as early as possible in order to prevent progression to critical ischemia since the prognosis at this stage is less favourable.

2.2.4 Risk Factors

Several modifiable risk factors are associated with PAD development, and these are similar to those for coronary artery disease (7). Fowler *et al.* found, in a study of 650 PAD cases and 3352 controls, that PAD was associated with smoking 1-14 cigarettes per day (odds ratio (OR) 3.9, 95% CI 2.7-5.6), with an even stronger association for smoking 25 or more cigarettes per day (OR 7.3, 95% CI 4.2-12.8) (13). There was a decrease in the OR for former smokers from 5.4 (95% CI 2.4-11.9) for less than 1 year to 1.3 (95% CI 1.0-1.7) for 20 years or more (13). In addition, there was an association between PAD and a history of diabetes mellitus (OR 1.9 95% CI 1.5-2.5), high triglycerides (OR 1.5 95% CI 1.1-2.0), high cholesterol (OR 1.3 95% CI 1.1-1.7) and physical inactivity (OR 1.4 95% CI 1.2-1.7). Dyslipidemia, obesity and hypertension (7) and above normal waist-to-hip ratio (OR 1.68 95% CI 1.05-2.70) (14) have also been shown to increase the prevalence of arterial disease. Selvin and Erlinger (2004), in a study of 2174 participants, also did not observe a difference in overall prevalence between the sexes; however, prevalence varied across age groups. (8).

Similar risk factors are associated with the development of intermittent claudication. The Framingham Heart Study followed 2336 men and 2873 women over the course of 38 years with biennial examinations (15). They performed an analysis of

risk factors for intermittent claudication (probability of having intermittent claudication at the 4 year follow up visit) as measured by the Rose Questionnaire (15). They found a significant association between intermittent claudication and: male sex (OR: 1.7, 95% CI: 1.3-2.1), age (OR: 1.5, 95% CI: 1.3-1.6 per 10 years), hypertension (stage 1 OR: 1.5, 95% CI: 1.1-2.0; stage 2 OR: 2.2, 95% CI: 1.7-3.0 compared to normotensive group), diabetes (OR: 2.6, 95% CI: 2.0-3.4), smoking (OR: 1.4, 95% CI: 1.3-1.5 per 10 cigarettes), cholesterol (OR: 1.2, 95% CI: 1.1-1.3 per 40mg/dL) and coronary heart disease (OR: 2.7, 95% CI: 2.2-3.4) (15). These are essentially the same risk factors as those mentioned previously for PAD.

2.2.5 Treatment

Goals surrounding the conservative clinical management of patients with PAD are to minimize disease progression and to optimize walking performance; with the long-term goal of minimizing limb loss (7).

Treatment of patients with PAD generally involves programs targeted at risk factor modification. Some of these programs include smoking cessation and exercise programs (7). In a study of 343 patients with intermittent claudication, smoking cessation reduced the risk of developing rest pain (0% in former smokers compared to 16% of those who continued to smoke after 7years) (16). A meta-analysis of treatment studies found that physical training increased pain free and total walking distance significantly (the measures were 139m, 95% CI 31-246.9 and 179.1m, 95% CI 60.2-298.1, respectively) (17). Medications can also be used in clinical management. These

include Pentoxifylline Ticlopidine, Clopidogrel, Cilostazol, Levocarnitine and Nafronyl (12). The effectiveness of these different medications in treating PAD or intermittent claudication varies (12,17). Most are targeted at risk factors (e.g.: cholesterol, hyperlipidemia) or at clot prevention via anti-platelet drugs (12,17). Revascularisation therapies are used to relieve ischemic symptoms and minimize tissue loss or limit the degree of amputation (7).

2.2.6 Assessment of walking performance

There are two ways to assess walking performance: 1) objective standardized walking tests and 2) self – report questionnaires.

2.2.6.1 Walking tests

Single stage (2mph constant grade 8-10%) and graded treadmill (2mph, increase in grade over time from 0%) tests have been used to determine a patient's walking ability (18). The distance of initial claudication distance (ICD: start of test to onset of pain) and absolute claudication distance (ACD: start of test to maximal pain, end of treadmill test) are typically used to describe walking performance in patients with claudication as these values are closely correlated over multiple visits in the graded test (18). In a study of 330 PAD patients with intermittent claudication for more than 6 months, the ACD, in comparison to the ICD, was a more reliable measure of exercise performance over multiple visits 3 months apart (ACD intra-class correlation coefficients were 0.90 and 0.88 for the graded and single stage tests; the ICD intra-class correlation coefficients were

0.81 and 0.74 for the graded and single stage tests) (19). The reliabilities of both the ACD and the ICD were higher for the graded treadmill test compared to the single stage test (19). In addition the authors reported that the reliability of the ACD for patients able to walk more than 300ft was similar for both treadmill tests (intra-class correlation coefficient 0.88 for graded versus 0.85 for single stage) whereas it was much higher for the graded test in patients unable to walk 300ft (0.83 versus 0.25 for the single stage) (19). These results indicate that for patients with severe walking impairment due to intermittent claudication the graded treadmill test is a more reliable measure of their walking performance; the single stage test may be adequate for those with limited intermittent claudication pain.

Functional claudication distance (FCD: the distance when the patient prefers to stop due to intermittent claudication) may be a more appropriate measure than the ICD and the ACD to evaluate a patient's walking ability, in day-to-day activities as, most patients will not stop walking after the onset of pain but will not walk until maximum pain is reached (20). In a study of 57 patients with intermittent claudication who received two treadmill tests 3 weeks apart, the reliability of the ACD was found to be greater than that of the FCD which in turn was greater than that of the ICD (intra-class correlation coefficients 0.97, 0.96 and 0.94, respectively) (20). The authors reported that the FCD, however, correlated best with quality of life followed by the ACD and the ICD (20) and suggested, therefore, that the FCD should be measured alongside the ICD and the ACD in a graded treadmill test (20).

Another test, the 6-minute walk test has also been used to assess walking performance (21). The 6-minute walk test measures the distance walked in 6 minutes at a patient's normal walking speed. In a study of 64 PAD patients, the distances walked during two 6-minute walk tests a week apart had a high reliability (intra-class correlation coefficient 0.94) (22). The 6-minute walking distance weakly correlated with the ICD ($r = 0.35$, $p = 0.007$) and moderately with the ACD ($r = 0.52$, $p < 0.001$) during a graded treadmill test (22). In a study of 34 PAD patients with intermittent claudication the 6-minute walk test was found to be more closely related to free-living physical activity, as measured with the energy expenditure of physical activity, than the ICD and the ACD ($r = 0.63$ $p < 0.001$ for the 6-minute walk test, $r = 0.27$ $p = 0.15$ for the ICD and $r = 0.47$ $p = 0.01$ for the ACD) (23). Another study with 156 PAD patients found that while the 6-minute walk test was significantly associated with higher levels of physical activity (p -trend = 0.01) the association was not significant between the ACD and physical activity (p -trend = 0.08) (24). Findings from these studies suggest that the 6-minute walk test may be a better measure of overall physical activity than the treadmill test in patients with intermittent claudication. The association, however, is really between the amount of physical activity performed throughout the day and the 6-minute walk test and not walking ability. In addition, neither study took into account the number of stops a patient makes during the day but simply how much physical activity they performed (23,24). Since by definition intermittent claudication is pain that resolves with rest, and this pain typically resolves rapidly (6,7) it is possible for patients with limited ability to still walk

large distances with numerous rests. These studies indicate, therefore, that the 6-minute walk test could be used as an estimate of a patient's physical activity but not for the primary assessment of walking ability.

While treadmill and the 6-minute walk test may provide insight into the severity of intermittent claudication, they may not be feasible in a clinical setting due to time constraints and willingness of the patient to participate. Self-report tools may therefore be more useful for the quick and effective assessment of a patient's severity of symptoms.

2.2.6.2 Self report assessment

Self report tools used in previous clinical and research studies include: the WHO/Rose Questionnaire (25), the Edinburgh Intermittent Claudication Questionnaire (25) and the *Walking Impairment Questionnaire* (26). The WHO/Rose Questionnaire (sensitivity 60%, specificity 91%) and the Edinburgh Intermittent Claudication Questionnaire (sensitivity 91.3%, specificity 99.3%) have been used to identify the presence of intermittent claudication (25) but do not provide information about the severity or impact of intermittent claudication.

The WIQ is the most commonly used self-report tool in this clinical population (27). It is a fourteen item tool used to evaluate limitation due to intermittent claudication (Figure 1). Total and subscale scores (distance, speed and stairs) are obtained. Each item is answered on a Likert scale from 0 for "unable to do" to 4 for "no difficulty" and weighted based on the difficulty of the task (e.g. the weight for "walk slowly" is 1.5 whereas for "run or jog" it is 5; full weights in Figure 1). Subscale scores are determined

by dividing the weighted answers by the maximum possible weighted score and multiplying by 100. Each score therefore ranges from 0-100 with lower scores indicating lower performance. The overall and combined scores are calculated as the average of the subscores. Items coded as “Didn’t do for other reasons” or missing are removed from the denominator of the weighted score to calculate a score based on the items that remain (i.e.: limitation, if any, was due only to intermittent claudication). If more than half of the items in a subscores are coded as such the subscore is coded as missing (28). An example of the scoring is included in the appendix.

The WIQ was first developed 20 years ago (26) and has been revised over time; thus the overall scores may not be comparable between studies (28). While the distance and speed scores have remained unchanged (save for changes from feet to metres for the Dutch version (29)) and scoring remains similar, three questions on stair climbing ability have been added and the section for differential diagnosis of PAD removed (28). In order to reduce the number of missing answers, the response option “Didn’t do for other reasons” was added (28). The modified questionnaire can be self-administered or phone-administered, with no significant difference in response between methods of administration (28).

Figure 1: The *Walking Impairment Questionnaire* with weights

For the following questions, the response options range from ‘No Difficulty’ to ‘Unable to Do.’ If you **cannot physically perform** a specified activity, for example walk 2 blocks without stopping to rest because of symptoms such as leg pain or discomfort, please place a ✓ in the box labeled ‘Unable to Do.’

However, if you **do not perform** an activity for reasons unrelated to your circulation problems, such as climbing a flight of stairs because your home is one level or your apartment has an elevator, please place a ✓ in the box labeled ‘Don’t Do For Other Reasons.’

- 1 Please place a ✓ in the box that best describes how hard it was for you to walk on level ground without stopping to rest for each of the following distances during the last week:

<i>During the last week, how difficult was it for you to:</i>	No Difficulty	Slight Difficulty	Some Difficulty	Much Difficulty	Unable to Do	Didn't Do for Other Reasons	Weight
a. Walk indoors, such as around your home?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	20
b. Walk 50 feet?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	50
c. Walk 150 feet? (1/2 block)?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	150
d. Walk 300 feet? (1 block)?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	300
e. Walk 600 feet? (2 blocks)?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	600
f. Walk 900 feet? (3 blocks)?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	900
g. Walk 1500 feet? (5 blocks)?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	1500

- 2 Please place a \surd in the box that best describes how hard it was for you to walk one city block on level ground at each of these speeds without stopping to rest during the last week. Please note 1 block is roughly equivalent to 300 feet.

<i>During the last week, how difficult was it for you to:</i>	No Difficulty	Slight Difficulty	Some Difficulty	Much Difficulty	Unable to Do	Didn't Do for Other Reasons	Weight
a. Walk 1 block slowly?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	1.5
b. Walk 1 block at average speed?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	2
c. Walk 1 block quickly?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	3
d. Run or jog 1 block?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	5

- 3 Please place a \surd in the box that best describes how hard it was for you to climb stairs without stopping to rest during the last week. Please note 1 flight of stairs is roughly equal to 14 steps.

<i>During the last week, how difficult was it for you to:</i>	No Difficulty	Slight Difficulty	Some Difficulty	Much Difficulty	Unable to Do	Didn't Do for Other Reasons	Weight
a. Climb 1 flight of stairs?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	1
b. Climb 2 flights of stairs?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	2
c. Climb 3 flights of stairs?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	3

2.2.6.3 Validation of the *Walking Impairment Questionnaire*

A small number of studies (Table 1) have described some evaluative aspects of the WIQ. The WIQ was developed and initially validated within a sample of 26 PAD patients with intermittent claudication able to walk on a treadmill (26). In this study, a change in the distance score was moderately associated with a change in the ICD ($r = 0.48$; $p < 0.05$) but not with a change in the ACD; a change in the speed score was moderately associated with a change in both the ICD ($r = 0.43$; $p < 0.05$) and the ACD ($r = 0.51$, $p < 0.05$) (26). A more recent study of 91 PAD patients with intermittent claudication reported that a change of 10% in the overall WIQ score corresponded to a change of the ACD of 345m. The study found a weak but significant correlation between the changes in the WIQ score and the ACD (Spearman's correlation coefficient = 0.33, $p = 0.004$) and a significant dependency of the change in WIQ score on the ACD (univariate linear regression analysis $p < 0.001$) (11). Findings from these studies indicate that changes in WIQ scores are modestly related to changes in walking performance as assessed with the ICD or the ACD.

Regensteiner *et al.* also assessed the correlation of the WIQ to the ACD and the ICD at the start of the study and following intervention (exercise program or revascularisation surgery) (26). They found that prior to intervention the distance score correlated moderately and significantly with the ACD ($r = 0.68$, $p < 0.05$) while the speed score did not. Following intervention, both distance and speed scores correlated moderately and significantly with the ACD ($r = 0.58$, $p < 0.05$ and $r = 0.67$, $p < 0.05$, respectively) as well as with the ICD ($r = 0.41$, $p < 0.05$ and $r = 0.40$, $p < 0.05$,

respectively). It is not clear why the association would change following intervention but it could be due to patient familiarity with the questionnaire and ruminating about it between administrations. The questionnaire was found to be repeatable (no change in scores for the control group) (26).

Another study of 48 patients with intermittent claudication found significant and moderate correlation between the distance score and the ACD (Spearman's rank correlation 0.41, $p < 0.05$) and the ICD (Spearman's rank correlation 0.35, $p < 0.05$) as measured using a single stage treadmill test (30). Yet another study with 130 patients with intermittent claudication and using a Dutch version of the questionnaire found that the distance, speed and stair climbing scores, as well as the total score, exhibited significant and weak to moderate correlations to both the ACD (0.45, 0.43, 0.37, 0.52 respectively, all $p < 0.01$) and the FCD (0.43, 0.45, 0.32, 0.48 respectively, all $p < 0.01$) (29). Thirty of these patients were used to evaluate the test-retest reliability which was determined to be highest for the overall WIQ score (intra-class correlation coefficient 0.89 for the total score versus intra-class correlation coefficient ranging from 0.75 to 0.8 for the three sections) (29).

These studies indicate that for patients reporting intermittent claudication, the WIQ score as well as some of its subscores appear to be significantly and moderately correlated with results from treadmill tests. These studies, however, may not adequately address the diverse nature of PAD and that many patients do not exhibit symptoms (e.g.: do not walk long enough to develop intermittent claudication or may truly have no

intermittent claudication yet may have significant PAD). Since the management of all levels of intermittent claudication is one of the goals for most PAD patients, understanding how patients with severe intermittent claudication differ from apparently symptomless patients and those with mild intermittent claudication is important in PAD research. The WIQ, therefore, needs to be validated for use with patients who experience a range of intermittent claudication symptoms.

The only study to investigate the validity of the WIQ in a diverse PAD population did so by comparing the results of the WIQ to the 4 metre speed test and 6-minute walk test, not a graded treadmill test (21). 146 PAD patients with and without intermittent claudication were assessed. The authors reported significant correlation between the WIQ distance score and the 6-minute walk test (Spearman's rank correlation coefficient 0.56, $p < 0.001$), and between the WIQ speed score and both the usual-paced and fast paced 4-metre walk test (Spearman's rank correlation coefficients 0.53 and 0.56 respectively, $p < 0.001$) (21). The associations between WIQ distance score and the 6-minute walk test for PAD patients with and without intermittent claudication, were similar when assessed via a regression analysis. (21). This supports the validity of the WIQ for use in a diverse population of PAD patients.

The samples used in previous studies conducted to evaluate the validity of the questionnaire range from 55.5% male to 96% male, with average ABIs ranging from 0.55 ± 0.2 to 0.72 ± 0.17 (11,21,26,29,30). These numbers indicate some obvious differences between the samples used previously. It is difficult to make recommendations

concerning the use of the questionnaire as the results from these studies may not be generalizable to the entire PAD population or even the population seen at the vascular clinic at KGH.

2.3 Summary

The primary goal of conservative clinical management of PAD is to minimize disease progression and optimize performance, it is, therefore, important clinically to be able to easily assess performance and the effects of treatment, including lifestyle modification, on walking performance. Walking performance has been assessed objectively via self-report tools or standardized treadmill tests (3,10,11,18-21,25,26,28,29). Treadmill tests are not always feasible in a clinical setting and a short self report tool such as the WIQ may be more useful. Previous studies investigating the WIQ all report on the correlation of the WIQ or its subscores to clinical measurements of walking ability (single stage treadmill test, graded treadmill test, 6-minute walk test or 4-metre walking test) but do not report on the true validity (sensitivity and specificity) of the WIQ vs. a gold standard and its ability to differentiate between groups of patients (e.g.: those with severe limitations compared to the others). These studies may not adequately address the diverse nature of the PAD population. We had the opportunity to address these gaps in the clinical research literature as well as to assess correlation between the WIQ and a graded treadmill test in a large PAD population.

Table 1: Summary of previous work on the validity of the *Walking Impairment Questionnaire* to evaluate walking ability in peripheral arterial disease patients

Authors (year) (ref)	Title	Sample	Study purpose	Evaluated against	Change or specific time	Key findings and Conclusions	Gaps or concerns
Regensteiner, J.G.; Steiner, J.F.; Panzer, R.J.; Hiatt, W.R. (1990) (26)	Evaluation of walking impairment by questionnaire in patients with peripheral arterial-disease	Limited to PAD patients with intermittent claudication (n = 26, 96% male)	To develop a questionnaire to evaluate the degree of walking impairment and efficacy of an intervention to improve walking ability	Graded Treadmill test: ACD	Change and specific time	<ul style="list-style-type: none"> • Moderate association of change in WIQ distance score with change in ICD • Moderate association of change in WIQ speed score with change in ICD and ACD • Moderate association of WIQ speed and distance scores with ICD and ACD • The WIQ is a valid instrument to characterize and detect changes walking impairment in patients with intermittent claudication 	Small sample size. Low female frequency
McDermott, M.M.; Liu, K.; Guralnik, J.M.; Martin, G.J.; Criqui, M.H.; Greenland, P. (1998) (21)	Measurement of walking endurance and walking velocity with questionnaire: validation of the <i>Walking Impairment Questionnaire</i> in men and women with peripheral arterial disease	Patients with PAD (ABI≤0.9) (n = 145, 55.5% male) patients without PAD (n = 65, 53.8% male)	To compare WIQ scores to objective measures of walking performance in a diverse population of PAD and non-PAD patients	Walking endurance with the 6-minute walk. Walking velocity with a 4-metre walk	Specific time	<ul style="list-style-type: none"> • Moderate association between the WIQ distance score and the 6-minute walk test • Moderate association between the WIQ speed score and the usual paced and fast paced 4m walk test • WIQ is a valid measure of community walking ability in a diverse group of patients 	Used the 6minute walk test and 4-metre speed test not a graded treadmill test. Sample of 55.5% males with PAD not representative of general distribution in population

Authors (year) (ref)	Title	Sample	Study purpose	Evaluated against	Change or specific time	Key findings and Conclusions	Gaps or concerns
Myers, S.A.; Johannig, J.M.; Stergiou, N.; Lynch, T.G.; Longo, G.M.; Pipinos, I.I. (2008) (30)	Claudication distances and the <i>Walking Impairment Questionnaire</i> best describe the ambulatory limitations in patients with symptomatic peripheral arterial disease	Limited to PAD patients with intermittent claudication (n = 48, % male unreported)	To evaluate the relationship between quantitative and qualitative measures of walking performance	Constant grade and speed treadmill test: ICD and ACD, Self selected pace treadmill test	Specific time	<ul style="list-style-type: none"> Moderate association between distance and pain scores and ICD and ACD WIQ is a valid tool to evaluate walking impairment in patients with intermittent claudication 	Small sample size and single stage treadmill test
Nicolai, S.P.; Kruidenier, L.M.; Rouwet, E.V.; Graffius, K.; Prins, M.H.; Teijink, J.A. (2009) (11)	The <i>Walking Impairment Questionnaire</i> : an effective tool to assess the effect of treatment in patients with intermittent claudication	Limited to PAD patients with intermittent claudication (n = 91, 61.5% male)	To evaluate the WIQ as a tool for detecting changes in daily walking ability	Graded treadmill test: ACD	Change	<ul style="list-style-type: none"> Weak correlation between change in the WIQ score and ACD WIQ is a valid tool to detect changes in the daily walking ability 	Did not look at validity at a specific time but rather whether is able to assess changes in ability following an intervention
Verspaget, M.; Nicolai, S.P.; Kruidenier, L.M.; Welten, R.J.; Prins, M.H.; Teijink, J.A. (2009) (29)	Validation of the Dutch version of the <i>Walking Impairment Questionnaire</i>	Limited to PAD patients with intermittent claudication (n = 130, 63% male)	To validate the Dutch version of the WIQ using European metric system	Graded treadmill test: ACD	Specific time	<ul style="list-style-type: none"> Moderate association between WIQ speed, distance and total scores and FCD and ACD The Dutch version of the WIQ using the European metric system is a valid, reliable and clinically relevant instrument for assessing walking impairment in patients with intermittent claudication 	Dutch Version of the questionnaire

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Chapter 3

Methods

3.1 Overview

Drs. Peter Brown, David Zelt, Ann Brown, Joan Tranmer, John Rudan and Robert Ross received funding from the Academic Health Science Centres Innovation Fund to develop a large clinical PAD cohort to systematically quantify, through detailed testing, modifiable factors associated with optimal patient outcomes. To address the thesis study objectives we conducted a discrete cross-sectional analysis of baseline characteristics of participants enrolled in the ongoing cohort study.

The overall goal of this research was to determine the validity of the *Walking Impairment Questionnaire* as a tool to identify high and low levels of walking ability in patients with PAD. Our specific objectives were:

- (A) To determine the criterion validity of the WIQ;
- (B) To determine cut-off scores for the WIQ to identify patients with low or high walking ability;
- (C) To provide suggestions for ongoing clinical use of the WIQ.

3.2 Ethical approval

The PAD study protocol (SURG-212-10) and this thesis specifically (EPID-342-11) were approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

3.3 Sample

3.3.1 Participant identification and selection

Consecutive patients diagnosed with PAD in the vascular clinic at Kingston General Hospital between May 2010 and May 2011, were identified by the two vascular surgeons. The identified patients were telephoned and were invited to return to the hospital for a study visit.

3.3.2 Inclusion and exclusion criteria

Inclusion criteria were (a) a resting Ankle-Brachial Index of ≤ 0.90 (clinical definition of PAD) and (b) informed consent.

Participants were excluded if they had (a) severe ischemia requiring intervention, (b) comorbid conditions that limit walking (angina, congestive heart failure, chronic obstructive pulmonary disease or severe arthritis), (c) wheel chair, cane or walker requirement (d) non-compressible arteries preventing use of the Ankle Brachial Index, and/or (e) severe cognitive impairment. The exclusion criteria were selected to ensure that the patient was able walk on a treadmill and that claudication due to PAD was the limiting factor for walking performance.

3.4 Measures

3.4.1 Treadmill test

The treadmill test used in this study involved protocols similar to those used in previous PAD studies (1,2) and consisted of a progressive, graded treadmill protocol (constant speed at 2 mph after initial increase, 0% grade initially with 2% increases in

grade every two minutes after the initial speed increase to a maximum of 10%) conducted until maximal claudication pain was reached or to a maximum duration of 30 minutes (about 1 mile). Participants were asked to identify distance of initial claudication (ICD, start of test to onset of pain), functional claudication distance (FCD, the distance when the participant prefers to stop due to intermittent claudication) and absolute claudication (ACD: start of test to maximal pain, end of treadmill test). These measures were used to quantify the severity of claudication. To allow participants to familiarize themselves with the treadmill, the initial speed was set to 1.1 mph and increased by 0.1 mph every 10 seconds for the first 90 seconds until the maximum speed of 2 mph was reached.

3.4.2 Walking Impairment Questionnaire

As previously described, the WIQ is a fourteen item tool used to evaluate limitation due to intermittent claudication in the PAD population (3). We obtained subscale scores (distance, speed and stairs) as well as overall and combined scores. Participants rated on a Likert scale from 0 for “unable to do” to 4 for “no difficulty” questions related to walking ability. Scores were weighted based on the difficulty of the task (e.g. the weight for “walk slowly” is 1.5 whereas for “run or jog” is 5; full weights in Chapter 2, Figure 1). If a patient’s answer for “around the home” was lower than for “50 feet” the score was changed to that of “50 feet” since it is likely that participants lowered their answer based on the presence of stairs in the house and not that the question referred to “level ground”. Subscale scores are determined by dividing the weighted answers by the maximum possible weighted score and multiplying by 100. Each score therefore ranged from 0-100 with lower scores indicating lower performance. The overall

and combined scores were calculated as the average of the subscores. Items coded as “Didn’t do for other reasons” or missing were removed from the denominator of the weighted score to calculate a score based on the items that remained (i.e.: limitation, if any, was due only to intermittent claudication). If more than half of the items in a subscore were coded as such the subscore was coded as missing (4).

3.4.3 Additional Variables

3.4.3.1 ABI

ABI was obtained from referral forms filled out by the vascular surgeons. The values for these forms were those obtained from previous vascular testing within six months of treadmill test. The lower of the two ABI (right and left) was used as the participant’s ABI.

3.4.3.2 BMI/ Waist circumference

Weight was measured using a medical weight scale in pounds while height was measured in feet. These values were converted to the metric system (Kg and m) to determine the participant’s body-mass index (weight over height squared). Waist circumference was measured at the top of the iliac crest using an anthropometric tape (5).

3.4.3.3 Self report variables

A number of variables were determined based on completion of a self report questionnaire. The paper questionnaire was completed by the participant who was instructed to select the answer they felt was most appropriate to them. The administrator

provided no guidance if asked further questions by the participant, to be consistent with all participants and not to influence their answers.

Smoking status was assessed based on the answers to question 16 of the demographic questionnaire relating to when a participant had quit smoking. Answering “I have never smoked” corresponded to a never smoked status, “I am a current smoker” to current smoker status and any other answer to former smoker. Missing values were completed using answers from question 12 to determine current smoking status (“daily” or “occasionally” corresponding to current) a negative answer on question 12 (“not at all”) in combination with a positive answer on question 13 (“have you ever smoked cigarettes daily?”) corresponded to a former smoker status. Questions relating to smoking were based on the Canadian Community Health Survey (6) and are appended.

Number of pack years was determined based on the number of cigarettes smoked daily (question 15) multiplied by the duration of smoking. Smoking duration was determined as the halfway point in the time intervals from question 14 (e.g. “3 to 5 years” corresponds to 4 years, “more than 20 years” corresponded to 30 years).

Age was defined as age on December 31st 2011 and was determined based on the participants’ self-reported birthday.

Diabetic status was obtained from a self-reported list of comorbid conditions.

3.5 Data

3.5.1 Data collection procedures

Participant testing was conducted in a research laboratory space affiliated with the office of Dr. Brown at the Kingston General Hospital.

Weight, height and waist circumference were measured and the participant completed the treadmill test. Either a nurse with expertise in exercise testing, or the candidate (a trained first responder, EMT and EMA) conducted all testing to ensure constant monitoring of participants for any sign of a potential adverse event. Additionally, at least one of the vascular surgeons was on-call at the hospital during all testing and standard hospital emergency procedures were in place should the situation require them. Following the treadmill test, the participant sat and completed the questionnaires.

Participants were compensated for parking and gas with twenty dollars, whether they completed all steps or not.

3.5.2 Data management

Participant information was stored, devoid of identifiable information, in a locked study office. Results from the questionnaires, treadmill test and other variables were entered into a secure database stored on a password protected computer in a locked study office. Three members of the study team including the research coordinator and the candidate had access to the study identification number key in order to contact participants for the scheduling of tests.

3.5.3 Statistical analyses

Analyses were conducted using SAS (Statistical Analysis Software, Version 9.2, SAS Institute, Cary, North Carolina, USA)

The sample was described using standard univariate statistics. Descriptive statistics were obtained for the initial, functional and absolute claudication distances as well as for subscores and combined scores for the *Walking Impairment Questionnaire*. Participants were divided into three groups by tertiles of their absolute claudication distance (low, medium and high). Comparison of ABI between those who participated and those contacted who did not participate was determined using two-sample independent t-tests to determine if there was a difference between those who participated and those who did not.

To describe the criterion validity of the WIQ scores we determined the Spearman's rank correlation coefficients between the WIQ subscores and combined scores and the absolute claudication distance. To further describe the WIQ scores we compared scores between males and females and between participants < 60 and ≥ 60 using two-sample independent t-tests.

Receiver operating characteristic (ROC) curves were created for each subscore and combined scores in 0.5 cut-off increments for identifying low and high walking ability. The area under the curve was calculated using the trapezoidal method (7). The cut-off values were identified for at least 0.8 sensitivity, 0.9 sensitivity, 0.8 specificity and 0.9 specificity. Positive and negative predictive values for the cut-offs of the score with the highest area under the ROC curve for 0.9 sensitivity for low performers and 0.9 specificity for high performers were calculated.

Ratios between ICD, FCD and ACD were calculated for each of the three ability groups and compared using ANOVA (post-hoc test: Bonferroni method) to determine differences between groups. T-tests were used to determine whether the mean ratios (ACD/ICD, FCD/ICD and ACD/FCD) were different from 1.

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Chapter 4

Determination of valid cut-off points for use of the *Walking Impairment Questionnaire* for the identification of walking ability in patients with peripheral arterial disease

Abstract

Objective: The validity of the *Walking Impairment Questionnaire* (WIQ) as a clinical tool for use by clinicians in the conservative management of patients with peripheral arterial disease (PAD) has not been well established. The objective of this study was to determine the validity of the WIQ as a tool to identify high and low walking ability in a diverse sample of patients with PAD.

Methods: We conducted a cross-sectional study and enrolled 132 new and existing PAD patients who consecutively attended the vascular clinic at Kingston General Hospital between May 2010 and May 2011. Patients with an Ankle Brachial Index ≤ 0.9 were approached for study inclusion. Participants were excluded if they had (a) severe ischemia requiring intervention; (b) comorbid conditions that limited walking (angina, congestive heart failure, chronic obstructive pulmonary disease or severe arthritis); (c) wheel chair, cane or walker requirement; (d) non-compressible arteries; and/or (e) severe cognitive impairment. Walking performance was assessed with the *Walking Impairment Questionnaire* (surrogate measure) and a standardized graded treadmill test (gold standard measure). Other study variables were obtained via questionnaire (age, sex, comorbid conditions and smoking status) or direct measurement (weight, height, waist circumference).

Results: 123 patients completed the treadmill test (70.7% males, mean age of 66.5 and mean ABI of 0.6 with range 0-0.9). The scores on the WIQ ranged from 0 to 100 and

absolute claudication distance (ACD) ranged from 0.03 to 0.98 miles. All WIQ subscale and overall scores were positively and moderately associated with the ACD (r_s values 0.63 to 0.68, $p < 0.05$). Based on the area under the curve of the receiver operating characteristics curve analysis, an overall WIQ score of 42.5 or less identified low performers (sensitivity 0.9, specificity 0.7, area under the curve 0.89) while a combined distance and stair score of 75.5 or more identified high performers (sensitivity 0.4, specificity 0.9, area under the curve 0.81).

Conclusions: Based on these findings, the WIQ, an easily administered self-report questionnaire, and the cutoffs identified could be used to quantify and classify walking ability in PAD patients, making this a potentially useful tool for clinicians to manage and monitor PAD patients.

4.1 Introduction

Peripheral arterial disease (PAD) is a prevalent chronic condition that increases with age, affecting 20% of patients over the age of 75 years, and is associated with an exceptionally high risk of cardiac and cerebrovascular events (1,2). Intermittent claudication, defined as the onset of pain in the leg or gluteal muscles with exertion which resolves with a few minutes of rest (1,2), is a sentinel symptom of PAD and, in most cases, indicative of disease severity (3). The prevalence and effects of claudication on walking performance vary within this population even for patients with similar clinical profiles (3). Given that the primary goal of conservative clinical management of PAD is to minimize disease progression and optimize performance, it is important clinically to be able to easily evaluate the effects of treatment, including lifestyle modification, on walking performance. Walking performance has been measured via self-report questionnaire tools or standardized treadmill tests (4-14). However, many clinicians may not use standardized measures and rely solely on patient's subjective responses to their questioning (personal communication, 2010, Zelt and Brown). Thus it is difficult to quantify, monitor and accurately assess performance across the continuum of this chronic condition.

Single stage and graded treadmill tests have been used within PAD patients to determine onset of pain and maximum distance walked as measurements of walking ability (5). While these tests may provide insight into the severity of claudication, they are not feasible to conduct in most clinical settings. The *Walking Impairment*

Questionnaire (15), is a fourteen item tool, designed to evaluate walking performance (10). Results from previous studies that have employed the WIQ as compared to treadmill testing as a measure of walking performance are limited by small sample sizes (e.g.: 26 patients (12)), inclusion of homogenous groups of patients with intermittent claudication (11-13,16) or focus solely on changes in walking performance following treatment (11). These studies may not have adequately addressed the diverse nature of the PAD population and the wide range of observed symptoms (10,13). Results are therefore not generalizable to the larger PAD population. The only study to investigate the validity of the WIQ in a diverse population did so by comparing the results to the 4 metre walking velocity and 6-minute walking score, not a graded treadmill test (10).

The validity of the WIQ as a clinical tool therefore remains in question. The primary aim of this study was to determine valid cut-off points for identifying patients with low and high walking ability, as indicated by the WIQ. Categorization of high and low performers, in combination with knowledge of a patient's clinical condition would allow clinicians to more effectively prescribe treatment strategies for patient's symptoms, monitor progress and make changes to patient management as needed.

4.2 Methods

4.2.1 Participant identification and selection

Our research protocol and consent forms were approved by the Queen's University Health Sciences Research Ethics Board. All consecutive PAD patients seen in the vascular clinic at Kingston General Hospital between May 2010 and May 2011, who

met the inclusion criteria were identified by two attending vascular surgeons. The identified patients were telephoned, consented and invited to return to the hospital for a study visit. The study design was cross-sectional and based upon the baseline component of an ongoing cohort study.

4.2.2 Inclusion and exclusion criteria.

Patients were included if they had a resting Ankle-Brachial Index (ABI) of 0.90 or less (clinical definition of PAD) (2). Participants were excluded if they had (a) severe ischemia requiring intervention, (b) comorbid conditions that limited walking (angina, congestive heart failure, chronic obstructive pulmonary disease or severe arthritis), (c) wheel chair, cane or walker requirement, (d) non-compressible arteries preventing use of the Ankle Brachial Index, and/or (e) severe cognitive impairment. The exclusion criteria were selected to ensure that the participant was able to walk safely on a treadmill, and to ensure that claudication due to PAD was the limiting factor for walking performance.

4.2.3 Treadmill test

The treadmill test used in this study was similar to protocols followed in previous PAD studies (17,18) and consisted of a progressive, graded treadmill protocol (constant speed at 2 mph after initial increase, 0% grade initially with 2% increases in grade every two minutes after the initial speed increase to a maximum of 10%) conducted until maximal claudication pain was reached or to a maximum duration of 30 minutes (about 1 mile). Participants were asked to identify the time and distance of absolute claudication (ACD: start of test to maximal pain, end of treadmill test). ACD was used to quantify the

severity of claudication. To allow participants to familiarize themselves with the treadmill, the initial speed was set to 1.1mph and increased by 0.1 mph every 10 seconds for the first 90 seconds until the maximum speed of 2 mph was reached. Participants were excluded from the analysis if they failed to complete the treadmill test to ACD (i.e.: the treadmill was stopped for reasons other than claudication, e.g.: shortness of breath).

4.2.4 *Walking Impairment Questionnaire.*

The *Walking Impairment Questionnaire* (15), contains 14 items and is used to evaluate limitations due to intermittent claudication. Three subscale scores are obtained: distance, speed and stair climbing ability. A copy of the questionnaire is appended. Each question was answered on paper by the participant who was instructed to select the answer they felt was most appropriate for them. The administrator provided no other guidance to the participant.

4.2.5 *Scoring the Walking Impairment Questionnaire.*

The WIQ is a fourteen item tool used to evaluate limitation due to intermittent claudication. Total and subscale scores (distance, speed and stairs) are obtained. Each item is answered on a Likert scale from 0 for “unable to do” to 4 for “no difficulty” and weighted based on the difficulty of the task (e.g. the weight for “walk slowly” is 1.5 whereas for “run or jog” it is 5; full weights and questionnaire are appended). If a patient’s answer for “around the home” was lower than for “50 feet” the score was changed to that of “50 feet” since it is likely that participants lowered their answer based on the presence of stairs in the house and not that the question referred to “level ground”. Subscale scores are determined by dividing the weighted answers by the maximum

possible weighted score and multiplying by 100. Each score therefore ranges from 0-100 with lower scores indicating lower performance. The overall and combined scores are calculated as the average of the subscores. Items coded as “Didn’t do for other reasons” or missing were removed from the denominator of the weighted score to calculate a percent score based on the items that remained (i.e.: limitation, if any, was due only to intermittent claudication). If more than half of the items in a subscores were coded as such the subscore was coded as missing (4).

4.2.6 Ankle Brachial Index

ABI was obtained from previous vascular testing, within 6 months of testing. The lower of the two ABI (right and left) was used as the participant’s ABI.

4.2.7 Anthropometric measurements.

Weight and height were measured using a medical scale to determine the participant’s body-mass index (weight over height squared). Waist circumference was measured at the top of the iliac crest using anthropometric tape (19)

4.2.8 Self report variables

Diabetic status (yes or no), smoking status (current, former or never) were self reported. Age was defined as age on December 31st 2011 and was determined based on the participant’s self reported birthday. Number of pack years was determined based on the number of cigarettes smoked daily divided by 20 (standard pack size) multiplied by the duration of smoking (number of packs smoked daily multiplied by the number of years).

4.2.9 Statistical analysis

The sample was initially profiled using conventional descriptive statistics. Estimates were obtained for absolute claudication distances as well as for subscores and combined scores for the *Walking Impairment Questionnaire*. Participants were then divided into thirds by their absolute claudication distance (low, medium and high). Comparison of ABI between those who participated and those contacted who did not participate were determined using two-sample independent t-tests. Receiver operating characteristic curves were generated for each subscore, and combined scores for identifying low and high walking ability (using 0.5 score increments). The area under the curve was calculated using the trapezoidal method (20). The cut-off values were identified for varying levels of sensitivity and specificity (at least 0.8 and at least 0.9). Positive and negative predictive values for the cut-offs of the score with the highest area under the ROC curve for 0.9 sensitivity for low performers and 0.9 specificity for high performers were calculated. .

4.3 Results

174 of the 438 PAD patients screened were deemed ineligible based on the exclusion criteria. Of the 262 eligible patients, 207 patients were contacted for inclusion. 132 patients consented and participated in testing. 8 participants stopped the test prior to the onset of claudication (e.g. due to shortness of breath) and an additional one stopped prior to maximum claudication. 123 patients were, therefore, included in the analysis (Figure 1).

4.3.1 Participant characteristics

Table I shows the characteristics of the PAD patients who participated in the study (n=123). There was no significant difference in ABI between those who participated and those contacted who did not participate (means 0.58 and 0.60 respectively).

4.3.2 Walking Impairment Questionnaire Scores

The subscale and overall WIQ scores, categorized according to the ACD tertiles are shown in Table II. Due to missing data, sample sizes vary for each of the subscores. The scores ranged from a 0 to 100. The scores increased consistently in patient groups with low to high performance, when categorized according to the ACD obtained via the graded treadmill test. Despite a large standard deviation in scores within each group, all comparisons achieved a high level of statistical significance. Significant differences were observed between scores for men and women for speed ($P=0.02$), but not for any of the other subscores, the overall score or the ACD. There were no significant differences for any of the scores between those under the age of 60 and those above. The associations between the ACD and WIQ scores, as determined by the Spearman's correlation coefficients were all strong ($r>0.5$) and statistically significant. Coefficients for the combined distance and stair score and the overall score were larger than 0.65.

4.3.3 Identifying cut-offs for low walking performance

The area under the curve of the receiver operating characteristics (ROC) curve provides information about the ability of a test to identify true positives and true negatives. The closer the area is to 1, the better the test at distinguishing between patient groups. The area under the curve values for the ROC ranged from 0.80 to 0.89 with the

value for the overall WIQ score providing the highest value (Table III, Figure 2). Based on this analysis, a WIQ overall score of less than or equal to 39 permitted identification of a low performer with a sensitivity of at least 0.8 while maximizing specificity. A WIQ overall score of 42.5 increases the sensitivity to at least 0.9 but decreases the specificity to 0.7. Similar cut-off values are shown for 0.8 specificity and 0.9 specificity in Table III.

4.3.4 Identifying cut-offs for high walking performance

The area under the curve values for the ROC ranged between 0.73 and 0.81, with the value for the combined distance and stair climbing ability being the highest (Table IV, Figure 3). A combined distance and stair climbing ability score of 58 permitted identification of a high performance with a specificity of at least 0.8. Choosing a cut-off of 75.5 increases the specificity to at least 0.9 but decreases the sensitivity to 0.4. Similar cut-off values are shown for 0.8 sensitivity and 0.9 sensitivity in Table IV. The area under the curve values for identifying high walking performance were lower than those for identifying low walking performance.

4.3.5 Predictive values

High negative predictive value is observed for low performers (0.94) while it is a lower for high performers (0.75). In both cases the positive predictive value is lower (0.62 for identifying low performers, 0.70 for identifying high performers).

4.4 Discussion

The ability to classify PAD patients accurately based on the severity of their claudication provides information relevant to conservative management of the disease (6).

In this study, only two out of eleven claiming to not have claudication did not experience any and that another two claiming to have claudication did not experience any, indicating the added importance of a screening objectively for patients' true claudication status. Treadmill tests and the 6-minute walk can be used to assess the severity of intermittent claudication exhibited by a patient. However, these tests are not routinely performed in clinical settings. The *Walking Impairment Questionnaire* (WIQ) is the most commonly reported self-report tool that has been used to evaluate changes in a patient's walking ability. This questionnaire had not been validated as an assessment tool for determining the impact of current intermittent claudication against a treadmill test in a large diverse PAD population (10,13). In this study, we determined cut-off values for the WIQ for low and high walking performance; information that could easily be used by clinicians to make more informed decisions concerning a patient's treatment plan.

The WIQ scores reported in this study are similar to those of previous studies which ranged from 38 to 55 for distance, 37 to 52 for speed and 48 to 68 for stair climbing (39.5, 47.6 and 58 respectively in this study) (10,11,13,16). ACD were also within the range of previous studies (mean of 181-460 m compared to 418 m in this study) however, these values may not be comparable due to differences in treadmill protocols (e.g.: constant grade versus graded treadmill tests) (10,11,13,16).

Regensteiner *et al.* assessed the correlation of the WIQ scores to the ACD in a sample of 26 patients: distance and speed scores correlated moderately and significantly with the ACD ($r = 0.58$, $P < 0.05$ and $r = 0.67$, $P < 0.05$ respectively) (12). Another study of 48 patients with intermittent claudication found significant and moderate correlation

between the distance scores and the ACD (Spearman's rank correlations 0.41, $P < 0.05$) (16). Another study with 130 patients with intermittent claudication, using a Dutch version of the questionnaire, reported similar correlations: distance, speed and stair climbing scores as well as the overall score were moderately correlated with the ACD (0.45, 0.43, 0.37, 0.52 respectively, all $P < 0.01$) (13). All scores were significantly correlated to the absolute claudication distance (ACD). Our data suggests that the overall WIQ score had the strongest association with the ACD, followed closely by distance and the three combined scores (all r values between 0.63 and 0.68). Correlation values in this study were similar to those of previous studies (12,13,16). Results from our study support the WIQ as a useful measurement of walking ability at a specific point in time in a diverse group of PAD patients.

4.4.1 Identification of high and low performers

Based on the area under the curve of the ROC, the overall score seems to be the most appropriate score for identifying low performers while the combined distance and stair score is the most appropriate for identifying high performers. The 95% confidence intervals of the area under the curve of the ROC, for all scores, for identifying low and high performers overlap indicating that there may not be a significant difference between the accuracy of a particular score or combination of scores. The accurate identification of low performers is important as these patients' symptoms and PAD may be progressing. It is therefore important to have low false negatives. This translates into a test for identifying low performers with high sensitivity. In our study, to obtain a sensitivity of at least 0.8 or at least 0.9 the cut-off values for the overall score were 39 (specificity = 0.77)

and 42.5 (specificity = 0.73) respectively. Thus, with a score of 42.5, less than 10 % of low performers would not have an overall score of 42.5 or less and less than 30% of non-low performers would have scores of 42.5 or less.

High performers may not require further invasive or different interventions as their current conservative management and lifestyle (i.e., exercise) is adequate. Therefore, it is important to have a test with high specificity for identifying high performers with low false positives to ensure that non-high performers are identified and receive the intervention they need. To obtain a specificity of at least 0.8 or at least 0.9 the cut-off values for the combined distance and stair score were 58 (sensitivity = 0.6) and 75.5 (sensitivity = 0.4) respectively. Less than 10% of non-high performers would have a combined distance and stair scores of 75.5 or more; however, 59% of high performers would be identified as being non-high performers with that same cut-off.

The cutoff value for identifying low performers has both high sensitivity and specificity (0.9 and 0.7). It also has a very high negative predictive value (0.94) but a lower positive predictive value (0.6) indicating that this score is very good at identifying low performers in this population but may result in the overtreatment of patients who are misclassified as low. The cutoff value for identifying high performers has high specificity (0.9) but low sensitivity (0.4). In this population it has high positive predictive value and high negative predictive value (0.70 and 0.75) indicating that, despite a low specificity, the cutoff may be effective at differentiating between high performers and non-high performers.

4.4.2 Strengths and limitations

The specific strengths of this study are as follows: validation testing in a large, clinically diverse patient sample reflective of the typical PAD population; comparison of the WIQ with a graded treadmill test; analysis of varied score combinations for the WIQ and detailed ROC curve analysis to determine potentially, clinically useful cut-off values which has not previously been done. There are limitations however. One limitation of the study comes from the questionnaire design itself. Over twenty participants answered that they perceived a higher level of difficulty walking around their home than walking 50 feet. Participants commented that in-home walking ability included stair climbing and this was more difficult than walking on level ground as the question states. Adjusting for this was, therefore, done as described in the methods. This does, however, highlight a problem with the questionnaire layout which may need to be addressed by comparing other presentations in the future or through continuing to modify the answers in the scoring as done here.

The population studied, while a diverse population of PAD patients (from severe impairment: ACD less than 0.1 miles to no claudication), is limited to individuals able to safely participate in a treadmill test and whose walking is limited by claudication and not other factors. This means that the generalizability of these results is restricted to this group. This may also be a strength of the study as it is generalizable to a group who could participate in an exercise intervention designed to alleviate symptoms and promote performance. A large number of patients either refused or were unable to participate. It is likely that those who refused were more compromised as they did not wish to

participate in a treadmill test. However, we were able to recruit patients with a wide range of walking ability: ACD less than 0.1 to 1 mile and a large number of patients with lower ability (right skew) so this may not be a limitation and there was no significant difference in ABI between those who participated and those contacted who did not participate. The high number of patients unwilling to participate in a treadmill test or unable to attend a test date does highlight the importance of a valid questionnaire with established cut-off points which could be used in future studies to increase participation rate.

4.4.3 Conclusions and future directions

Our results indicate that the WIQ has an acceptable level of sensitivity and specificity for the assessment of walking ability in a diverse population of patients able to safely participate in a treadmill test. Potential cut-offs have been identified for determining whether a patient has low or high walking ability. These cut-offs combined with other patient characteristics should be one component of a clinical decision rule, to guide patient management. The WIQ could also be used in large epidemiological studies to identify low and high walking ability. Further research could consider development and validation of revised and shorter versions of the WIQ in similar patient populations. As well, a cohort or longitudinal study of patients with the recommended cutoffs could be conducted to assess the prognostic potential of the WIQ.

Figure1. Participant flow

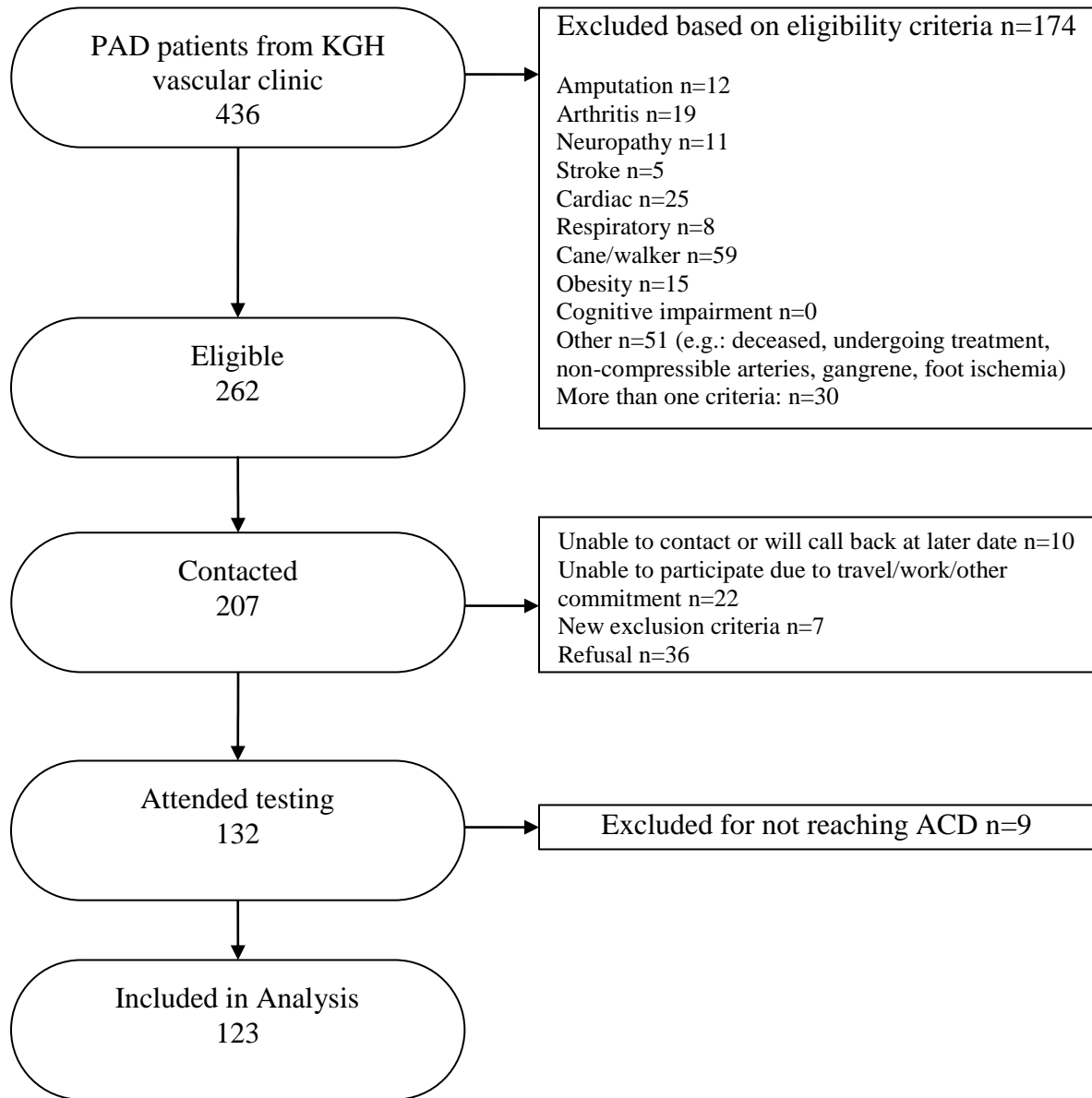


Table I: Baseline characteristics of participants categorized by walking performance

Characteristics	Total
N	123
Age (years) – mean (SD)	66.5 (9.4)
Male sex – %	70.7
ABI - mean (SD)	0.6 (0.2)
BMI (kg/m ²) - mean (SD)	28.0 (5.6)
Waist circumference (inches)- mean (SD)	38.6 (5.0)
Current smoker – %	31.4
Former smoker – %	65.3
Never smoked – %	3.3
Pack years – mean (SD)	23.8 (14.3)
Diabetes - %	22.8

SD: Standard deviation, ABI: Ankle Brachial Index, BMI: Body Mass Index

Table II: Absolute claudication distance and WIQ scores categorized by walking performance

	n	Low		Medium		High		Total		P
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Absolute claudication distance (miles)	123	0.06	0.02	0.18	0.05	0.53	0.26	0.26	0.25	<0.0001*
WIQ – Distance	119	18.3	19.4	38.4	25.3	59.7	27.8	39.5	30.2	<0.0001*
WIQ – Speed	119	27.9	20.6	49.9	25.8	61.3	24.9	47.6	28.0	<0.0001†
WIQ – Stair	109	37.5	21.3	61.4	26.9	73.8	23.0	58.0	27.8	<0.0001†
WIQ - Distance and speed	115	23.2	19.2	44.6	22.0	60.1	23.7	39.5	30.2	<0.0001*
WIQ – Overall	102	26.9	13.8	52.0	21.2	65.0	20.6	47.6	28.0	<0.0001*

ACD: Absolute claudication distance, SD: Standard deviation

Low, Medium, High categories are based on thirds of the population divided by tertiles of ACD

P-value: ANOVA test

*: significant difference between all groups using Bonferroni method

†: significant difference between all groups except medium and high using Bonferroni method

Note: Sample sizes vary for each subscore based on the number who had fewer than half missing values for that subscores. If any of the subscores were missing the overall score was coded as missing.

Table III: Cut-offs for the WIQ subscores and combined scores for various sensitivity and specificities as well as the area under the curve of the ROC for identifying those in the low walking performance group

	0.8 sensitivity		0.9 sensitivity		0.8 specificity		0.9 specificity		Area under the curve of the ROC (95% CI)
	Cutoff	Specificity	Cutoff	Specificity	Cutoff	Sensitivity	Cutoff	Sensitivity	
Distance	28.5	0.73	38.5	0.57	25.0	0.73	15.5	0.62	0.83 (0.75-0.91)
Speed	39.5	0.66	58.0	0.39	35.5	0.66	24.5	0.50	0.81(0.72-0.90)
Stair	54.5	0.65	67.0	0.47	41.5	0.47	29.0	0.33	0.81 (0.73-0.89)
Distance and speed	33.5	0.73	44.5	0.57	30.5	0.74	27.0	0.69	0.85 (0.77-0.93)
Distance and stair	39.0	0.76	47.0	0.69	36.0	0.76	28.5	0.48	0.86 (0.79-0.93)
Speed and stair	44.0	0.79	50.0	0.69	42.5	0.74	32.5	0.53	0.88 (0.81-0.94)
Overall	39.0	0.77	42.5	0.73	35.0	0.72	32.5	0.66	0.89 (0.82-0.95)

ROC: Receiver operating characteristics

CI: Confidence Interval

The shaded score has the highest area under the curve of the ROC

Figure 2: Sample ROC curve for identifying low performers: ROC curve for the overall score on the WIQ

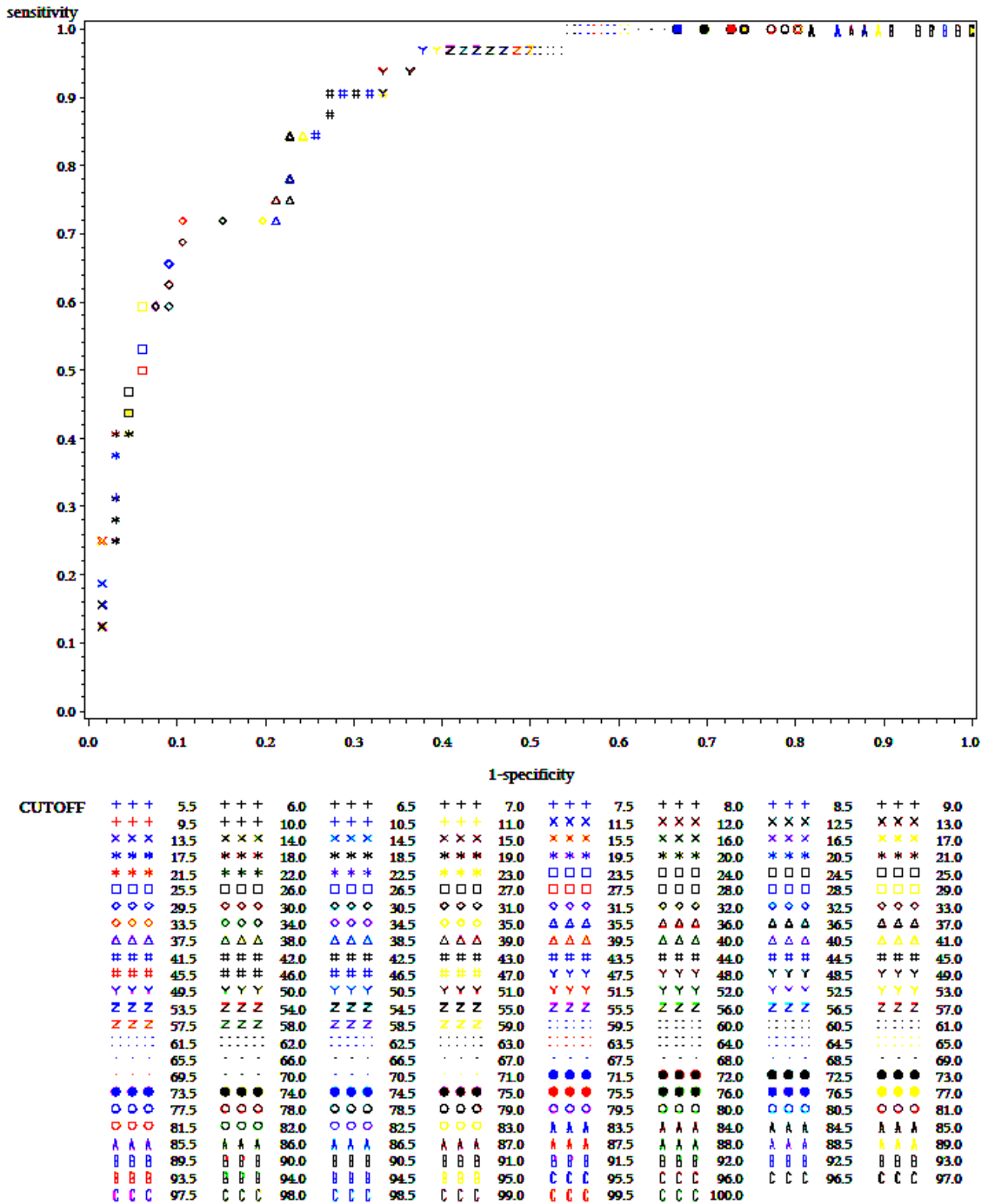


Table IV: Cut-offs for the *Walking Impairment Questionnaire* subscores and combined scores for various sensitivity and specificities as well as the area under the curve of the ROC for identifying those in the high walking ability group

	0.8 sensitivity		0.9 sensitivity		0.8 specificity		0.9 specificity		Area under the curve of the ROC
	Cutoff	Specificity	Cutoff	Specificity	Cutoff	Sensitivity	Cutoff	Sensitivity	
Distance	30.5	0.63	19.0	0.42	44.0	0.66	62.0	0.45	0.80 (0.72-0.89)
Speed	39.0	0.55	31.5	0.44	57.5	0.49	83.0	0.26	0.74 (0.65-0.83)
Stair	54.0	0.51	41.5	0.36	67.0	0.60	87.5	0.23	0.76 (0.66-0.85)
Distance and speed	36.0	0.63	28.0	0.44	53.0	0.50	64.0	0.47	0.78 (0.70-0.87)
Distance and stair	47.0	0.68	38.0	0.56	58.0	0.62	75.5	0.41	0.81 (0.73-0.90)
Speed and stair	48.0	0.61	36.0	0.38	64.0	0.57	75.0	0.46	0.78 (0.69-0.88)
overall	44.0	0.67	34.0	0.47	61.0	0.53	69.5	0.47	0.80 (0.72-0.89)

ROC: Receiver operating characteristics

CI: Confidence Interval

The shaded score has the highest area under the curve of the ROC

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Appendix: The *Walking Impairment Questionnaire* with weights

For the following questions, the response options range from 'No Difficulty' to 'Unable to Do.' If you **cannot physically perform** a specified activity, for example walk 2 blocks without stopping to rest because of symptoms such as leg pain or discomfort, please place a ✓ in the box labeled 'Unable to Do.'

However, if you **do not perform** an activity for reasons unrelated to your circulation problems, such as climbing a flight of stairs because your home is one level or your apartment has an elevator, please place a ✓ in the box labeled 'Don't Do For Other Reasons.'

- 1 Please place a ✓ in the box that best describes how hard it was for you to walk on level ground without stopping to rest for each of the following distances during the last week:

<i>During the last week, how difficult was it for you to:</i>	No Difficulty	Slight Difficulty	Some Difficulty	Much Difficulty	Unable to Do	Didn't Do for Other Reasons	Weight
a. Walk indoors, such as around your home?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	20
b. Walk 50 feet?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	50
c. Walk 150 feet? (1/2 block)?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	150
d. Walk 300 feet? (1 block)?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	300
e. Walk 600 feet? (2 blocks)?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	600
f. Walk 900 feet? (3 blocks)?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	900
g. Walk 1500 feet? (5 blocks)?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	1500

- 2 Please place a \surd in the box that best describes how hard it was for you to walk one city block on level ground at each of these speeds without stopping to rest during the last week. Please note 1 block is roughly equivalent to 300 feet.

<i>During the last week, how difficult was it for you to:</i>	No Difficulty	Slight Difficulty	Some Difficulty	Much Difficulty	Unable to Do	Didn't Do for Other Reasons	Weight
a. Walk 1 block slowly?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	1.5
b. Walk 1 block at average speed?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	2
c. Walk 1 block quickly?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	3
d. Run or jog 1 block?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	5

- 3 Please place a \surd in the box that best describes how hard it was for you to climb stairs without stopping to rest during the last week. Please note 1 flight of stairs is roughly equal to 14 steps.

<i>During the last week, how difficult was it for you to:</i>	No Difficulty	Slight Difficulty	Some Difficulty	Much Difficulty	Unable to Do	Didn't Do for Other Reasons	Weight
a. Climb 1 flight of stairs?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	1
b. Climb 2 flights of stairs?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	2
c. Climb 3 flights of stairs?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/>	3

Chapter 5

Additional results

This chapter provides additional findings pertaining to the *Walking Impairment Questionnaire* and the treadmill test. These results were not included in the manuscript. The analyses were completed to address the stated thesis objectives.

5.1 Objective 1: Further analysis of WIQ validity

Univariate statistics for the WIQ subscores are shown in Table 1.

A significant difference between scores for men and women was observed for the speed and combined speed and distance scores but not for any of the other subscores or the overall score (Table 2). No significant difference was observed for any of the scores between those under the age of 60 and those above (Table 2). The mean scores in men and older persons are, however, consistently higher than for females and younger persons respectively, irrespective of significance.

Spearman's correlation coefficients are shown in Table 3. For the entire sample all correlation coefficients were larger than 0.5 and both the combined distance and stair score and the overall score were larger than 0.65. For males alone, all correlation coefficients were larger than 0.65 except for the speed score ($r = 0.58$). Correlation coefficients were significant for all subscores, combined scores and overall score relative to the absolute claudication distance, except for female stair climbing ability. Correlation coefficients were higher for males than females for all scores except speed.

5.2 Objective 3: Further analysis to support clinical utility

132 individuals participated in this study, however, 8 participants stopped the test prior to the onset of claudication (e.g. due to shortness of breath) and an additional one

stopped prior to maximum claudication. Therefore the sample size for ICD is 124 and for ACD is 123. Only 102 (83% of those who reached ACD) of the participants identified their time of functional claudication, that is the time at which they would prefer to stop. Means for ICD, FCD and ACD are significantly different between all groups ($P < 0.001$) (Figure 1). Eleven patients claimed not to have claudication according to the vascular surgeons. Of these only one did not experience claudication during the treadmill test. Two patients claiming to have intermittent claudication did not experience claudication during the treadmill test.

To describe the walking performance group differences we determined the ratio of ACD to FCD, ACD to ICD and FCD to ICD. The ratio of ACD to FCD is 1.2 in both the low and medium groups (not significantly different between groups) however the ratio of ACD to FCD is significantly different for the high group at 1.7 times (Table 4). The ratio of FCD to ICD is 1.8, 2.3 and 3.0 respectively for the low, medium and high groups yet only the Low and High groups are significantly different. The ratio of ACD to ICD is 2.2, 3.1 and 4.6 respectively for the low, medium and high groups yet only the Low and High groups are significantly different. In all cases the mean ratio is significantly different from 1.

Sensitivity, specificity as well as positive and negative predictive values are shown along with two by two tables for the two cutoffs identified in the manuscript (Table 5 a and b). High negative predictive value is observed for low performers (0.94) while it is a lower for high performers (0.75). In both cases the positive predictive value is lower (0.62 for identifying low performers, 0.70 for identifying high performers).

Table 1: Scores of the *Walking Impairment Questionnaire*

	n	mean	SD	min	max	median
Distance	119	39.5	30.2	0.9	100.0	31.8
Speed	119	47.6	28.0	0.0	100.0	43.5
Stair	109	58.0	27.8	4.2	100.0	58.3
Distance and speed	115	44.0	27.0	1.5	100.0	38.8
overall	102	48.8	24.7	5.5	100.0	45.5

SD: Standard deviation

Note: Sample sizes vary for each subscore based on the number who had fewer than half missing values for that subscores. If any of the subscores were missing the overall score was coded as missing

Table 2: Scores of the *Walking Impairment Questionnaire* by sex and age groups

	n	Sex					Age				
		Female		Male		P	< 60 yrs		>= 60		P
		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Distance	119	34.8	31.5	41.1	29.7	0.31	31.6	26.4	41.7	30.9	0.13
Speed	119	37.6	27.8	51.3	27.2	0.02	39.1	22.6	49.8	28.9	0.10
Stair	109	56.4	27.3	58.5	28.1	0.73	51.0	27.5	59.9	27.7	0.17
Distance and speed	115	36.1	28.5	46.7	26.0	0.06	35.5	23.0	46.2	27.6	0.08
overall	102	43.1	23.3	50.5	25.0	0.20	40.5	23.5	51.2	24.7	0.07

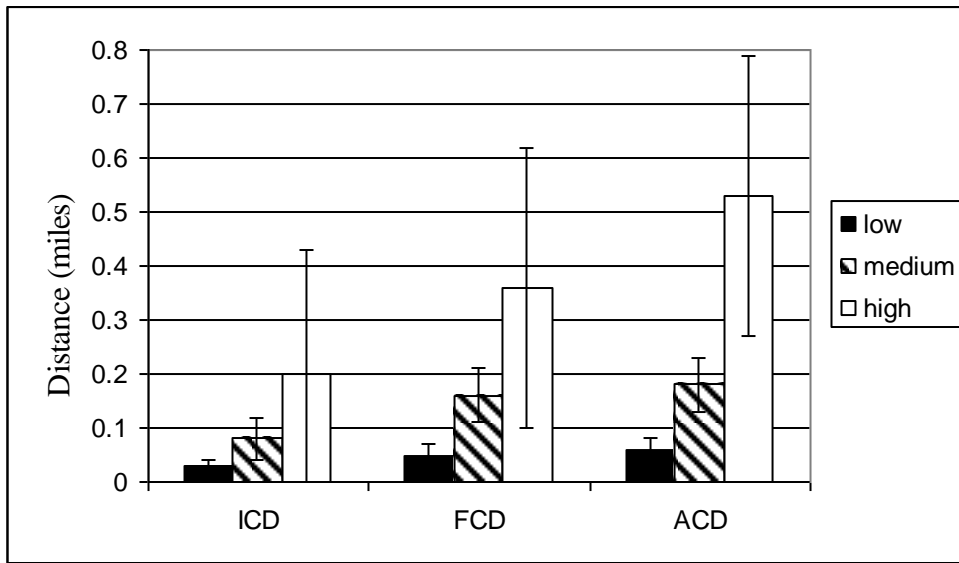
SD: Standard deviation

P-value: independent t-test

Table 3: Spearman's Correlation Coefficients of the scores of the *Walking Impairment Questionnaire* relative to the absolute claudication distance for males, females and the whole population

		Male	Female	All
Distance	r	0.68	0.57	0.64
	p	<.0001	0.001	<.0001
	n	84	30	114
Speed	r	0.58	0.61	0.56
	p	<.0001	0.0003	<.0001
	n	83	31	114
Stair	r	0.66	0.15	0.53
	p	<.0001	0.47	<.0001
	n	77	27	104
Distance and Speed	r	0.68	0.59	0.63
	p	<.0001	0.0009	<.0001
	n	81	29	110
Distance and Stair	r	0.72	0.46	0.66
	p	<.0001	0.02	<.0001
	n	76	24	100
Speed and Stair	r	0.69	0.54	0.64
	p	<.0001	0.006	<.0001
	n	76	25	101
Overall	r	0.72	0.62	0.68
	p	<.0001	0.002	<.0001
	n	75	23	98

Figure 1: Treadmill test distances categorized by walking performance



Low, Medium, High are based on thirds of the population divided by tertiles of ACD
Error bars represent the standard deviations.

Sample size for ICD is 124, for FCD is 102 and for ACD is 123.

P-value: ANOVA test (all $P < 0.0001$)

t-test: means for ICD, FCD and ACD are significantly different between all groups ($P < 0.001$)

Table 4: Distance ratios for the treadmill test.

	Low		Medium		High		Total		ANOVA	Bonferroni method: significantly different groups
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P	
FCD/ICD	1.8	0.6	2.6	2.3	3.0	2.0	2.4	1.8	0.04	Low-high
ACD/FCD	1.2	0.2	1.2	0.3	1.7	1.2	1.4	0.7	0.006	Low-high, medium-high
ACD/ICD	2.2	0.8	3.1	2.6	4.6	3.9	3.3	2.9	0.0007	Low-high

t-test mean=1: all P<0.005

Table 5: Sample two by two tables for identifying low and high walking ability using the walking impairment questionnaire compared to the treadmill test.

Table 5.a uses a cutoff of 42.5 WIQ overall score to identify low performers.

Table 5.b uses a cutoff of 75.5 WIQ combined distance and stair score to identify high performers

5.a)

		Treadmill		
		Low	Not Low	Total
WIQ	Low	29	18	47
	Not Low	3	48	51
	Total	32	66	98

Sensitivity: 0.91 (0.81-1.00)
 Specificity: 0.73 (0.62-0.83)
 Positive predictive value: 0.62 (0.48-0.76)
 Negative predictive value: 0.94 (0.88-1.00)

5.b)

		Treadmill		
		High	Not High	Total
WIQ	High	14	6	20
	Not High	20	60	80
	Total	34	66	100

Sensitivity: 0.41 (0.25-0.58)
 Specificity: 0.91 (0.84-0.98)
 Positive predictive value: 0.70 (0.50-0.90)
 Negative predictive value: 0.75 (0.66-0.84)

Chapter 6

Discussion

Many of the results presented in this thesis are discussed in Chapter 4 (the manuscript). This chapter, therefore, will summarize and synthesize the key findings from both Chapters 4 and 5.

6.1 Summary of study

We conducted a cross-sectional study of 132 consecutive PAD patients from the vascular clinic at Kingston General Hospital for the 13 months ending May 2011 (the actual sample size for each measure varies: $n_{ICD}=124$, $n_{FCD}=102$, $n_{ACD}=123$). All patients (new and existing) who met the clinical inclusion criteria were approached for study inclusion. Walking performance was assessed with the *Walking Impairment Questionnaire* (surrogate measure) and a standardized graded treadmill test (1) (gold standard measure).

The overall goal of this research was to determine the validity of the *Walking Impairment Questionnaire* as a tool to identify high and low walking ability in patients with PAD. Our specific objectives were:

- (A) To determine the criterion validity of the WIQ;
- (B) To determine cut-off scores for the WIQ to identify patients with low or high walking ability;
- (C) To provide suggestions for clinical use of the WIQ.

6.2 WIQ: a potentially useful clinical tool

The main finding of this study is that we were able to identify cut-off values for the WIQ to permit the valid classification of patients based on a gold standard measure of their walking performance. Our findings suggest that patients who score 42.5 or less overall on the WIQ be classified as ‘low walking performers’ and 75.5 or more on the combined distance and stair score be classified as ‘high walking performers’. Based on our methodology, these cutoff scores have high sensitivity for identifying low performers and high specificity for identifying high performers.

Low walking performers may require more treatment than others and may require it more immediately. Lack of treatment could lead to the worsening of their symptoms and PAD more rapidly than others. It is therefore important to have low false negatives. This translates into a test for identifying low performers with high sensitivity. High performers may not require further intervention since it is likely that an intervention will have less of an effect on these individuals and continuing current treatment regime may be adequate. For ‘high walking performers’ it is important to have low false positives so that those requiring intervention receive it (the true negatives). For this reason it is important that the test for identifying high performers has a high specificity.

The cutoff value for identifying low performers has both high sensitivity and specificity (0.9 and 0.7). It also has a very high negative predictive value (0.94) but a lower positive predictive value (0.6) indicating that this score is very good at identifying low performers in this population but may result in the overtreatment of patients who are misclassified as low. The cutoff value for identifying high performers has high specificity (0.9) but low sensitivity (0.4). In this population it has high positive predictive

value and high negative predictive value (0.70 and 0.75) indicating that, despite a low specificity, the cutoff may be effective at differentiating between high performers and non-high performers.

The WIQ items all seem to be valid indicators of walking ability: correlations between ACD and WIQ scores are strong and significant. As discussed in the manuscript the correlation values observed in this study fall within the range observed in previous work on the WIQ and the ACD (2-4) reinforcing the criterion validity of the questionnaire established in previous studies. Our correlation values are on the upper end of the published range. Higher correlation in this study could be explained by differences between versions of the questionnaire. Another factor which may have led to higher correlation for answers relating to distance is that the treadmill test was performed prior to the administration of the WIQ, which may have provided participants with a more accurate perception of their ability directly prior to answering the questionnaire. This does not account for the higher correlation of speed or stair climbing ability scores as the treadmill test would not provide them with information concerning this. It may, however, be interesting to randomly allocate patients to questionnaire administration before or after treadmill test and compare correlation between these two groups in future studies.

Despite the high correlations between the WIQ scores and the ACD, there are some limitations to the questionnaire. There was a large proportion (22.7%) of individuals who had missing overall scores. This is due to the number who had missing subscores in any of the categories due to either too many missing values or values coded as “didn’t do for other reason”. It is unclear, at this time, why such a large proportion failed to fill out the questionnaire adequately to obtain an overall score, but it could be due to patient misunderstandings of the questions and failure to answer them with comprehension. For

example, a few patients believed they only had to answer one item per subsection and simply indicated the item at which they began to have difficulty (e.g. no answer for 1 or 2 flights but “much difficulty” for 3 flights). In addition, as described in the manuscript, over twenty participants answered a higher level of difficulty walking around their home than walking 50 feet. This was likely due to the participants considering the stairs in their house when determining their level of difficulty. The questionnaire does state that walking is on level ground, yet some participants failed to take this into consideration. The high number of missing overall scores and the high number who inappropriately answered the in-home distance item suggest a need to review the layout of the questionnaire, and possibly reword some of the items or continue to adjust for misinterpretation of the in-home item in the scoring.

There were no significant differences between scores for males and females on any of the scores except those for speed and for speed and distance combined. Mean scores are consistently higher for males than females and absence of significance may be due to lack of power to do this comparison. In addition, correlation coefficients are higher for males than females for all scores except speed and are all significant for males while stair climbing ability is not for females. This would indicate that stair climbing ability score in women is not correlated with walking performance as it is in men. These differences may indicate the need to determine different cut-offs for males and females for the questionnaire in a study with a larger sample size. However, differences in correlation may also simply be due to the sample being only about 30% female and therefore may not be accurate representation of the correlation in this group.

ACD was not significantly different between males and females indicating that differences picked up by the WIQ may be linked to perception of walking ability rather than actual ability. While the cutoffs identified here are effective at identifying those with high and low walking ability it would be interesting to determine, in future studies, whether the same cutoffs hold for both sexes or whether different cutoffs with higher sensitivity/specificity can be identified for each group.

6.3 Treadmill test results

The clinical importance of knowing a patient's walking ability has been previously outlined in this thesis. In this study, only two out of eleven claiming to not have claudication did not experience any and that another two claiming to have claudication did not experience any, indicating the added importance of a screening objectively for patients' true claudication status.

In addition to the information stated previously, results from this study outline an additional point. Not only are the mean ACD, ICD and FCD significantly different between the low, medium and high groups (increasing from low to high) but the mean ratios (ACD/FCD, ACD/ICD and FCD/ICD) are also significantly different between groups (some only between low and high). In addition, mean distance ratios increase from low to medium to high performers (save for ACD/FCD between low and medium). For example, the ACD to ICD ratio in the low group was 2.2 while in the high group it was 4.6. This may suggest that moving from the low to the high group not only increases the distance to onset of pain but improves the ability to walk following the onset of pain and relative to the onset of pain. These results highlight the importance of helping a patient to improve their walking performance and how much of an effect progression

between groups could have. Furthermore, while the ACD to FCD ratio are significantly different from 1 in all groups, the ratio remains small in the low and medium groups (ACD on average 1.2 times FCD) but is larger in the high group (1.7) indicating an increased ability in the high group to push oneself past where one would usually stop and may indicate a higher pain tolerance in this group. One patient described his pain during the test as increasing until he reached a certain point and then it began to decrease. He identified both an ICD and an FCD but walked the full thirty minutes never reaching ACD. This anecdote may indicate a difference in some of the patients in the high group. This study does not allow us to determine what the difference is but shows the need to continue to study these patients to fully understand PAD and its associated symptoms.

6.4 Strengths and Limitations

The sample used in this study was a diverse sample of PAD patients able to safely participate in a treadmill test. ABIs ranged from 0 to 0.9 with a mean of 0.6 showing the full range of occlusion. Additionally, patients had full ranges of scores for the WIQ (0-100) and ACD ranged from 0.03 miles to close to a mile indicating a full range of symptoms (severe claudication to apparent absence of claudication).

To our knowledge, previous studies have looked only at individual subscores and the overall score and have neglected to consider other combinations of subscores (2-6). Had we not used new combinations of scores, it is likely that the distance score alone would have been selected to identify high performers and the test would have had lower area under the curve of the ROC. The 95% confidence intervals of the area under the curve of the ROC, for all scores, for identifying low and high performers overlap indicating that there may not be a significant difference between the accuracy of a

particular score or combination of scores. This indicates that the combined scores should continue to be investigated as they may be useful in the identification of high and low performers but that additional studies with larger sample sizes should be conducted to confirm this finding.

As described previously, two limitations of this study are the lack of emphasis on the flat ground aspect for the distance questions and the possible issue of high number of refusals to participate. The former was dealt with in the analysis stage and may suggest that the layout of the questionnaire needs to be revisited. The latter illustrates one aspect of the difficulty with a treadmill test in this population. A valid tool to evaluate walking ability and reduce the participation refusal rate is, therefore, important.

6.5 Implications

Our results indicate that the WIQ has sufficient validity to assist in the assessment of walking ability in a diverse population of patients able to safely participate in a treadmill test. Previous studies have also determined that the WIQ can identify changes in walking ability (3,6). This suggests therefore that the WIQ is a clinically useful tool to identify patients' walking abilities at a specific point in time. It may be used as one part of a tool to help clinicians to determine a course of treatment based on this ability, and then monitor the patient and determine the effectiveness of treatment

Cutoffs have been identified for determining whether a patient has low or high walking ability. Based on this research we would suggest 42.5 or less overall score to identify patients with low walking ability and 75.5 or more combined distance and stair score identify patients with high walking ability. These cut-offs, combined with other

patient characteristics, should assist clinicians in selecting the most appropriate course of treatment for each PAD patient.

The WIQ could also be used in large epidemiological studies to identify low and high walking performance. The WIQ is a short questionnaire, easily filled out and easily scored while treadmill tests are more expensive, more time consuming and likely contribute to higher rates of refusals to participate. Using the WIQ instead of treadmill tests may make large epidemiological studies of PAD patients more feasible, and could therefore provide increased insight into this population.

6.6 Future research

6.6.1 Modified tool

Further research could consider development and validation of revised and shorter versions of the WIQ in similar patient populations. For example the speed subscore could be dropped if one is only interested in determining whether an individual is a high performer or not. Revised layouts could also be investigated to reduce the number of missing subscores and overall scores.

6.6.2 Validation of cut-off values

It may be worthwhile to differentiate between males and females, in future studies, to determine whether the same cut-offs hold for both sexes, since correlation between scores and ACD and the scores themselves appear to differ between them.

As well, a cohort or longitudinal study of patients with the recommended cutoffs could be conducted to assess the prognostic potential of the WIQ. These studies could help with clinical decision rule development.

6.6.3 Interventional research

Interventional studies are currently beginning as part of the greater PAD project to determine the effect of an exercise intervention on walking performance. The WIQ, as a tool which can evaluate both ability at a specific point in time and changes in ability, is well suited for interventional studies. Participants could easily fill out the questionnaire at regular intervals without having to come in for a lengthy treadmill test.

6.7 Conclusion

The specific objectives of this study were met:

(A) Our results indicate that the WIQ has test properties consistent with high validity for assessing walking ability in a diverse population of patients able to safely participate in a treadmill test at a specific point in time.

(B) We would suggest a 42.5 or less overall score to identify patients with low walking ability and a 75.5 or more combined distance and stair score to identify patients with high walking ability.

(C) We suggest using the WIQ instead of a treadmill test when a treadmill test is not feasible to identify a patient's walking ability based on the cutoffs listed above.

In addition to these specific objectives our study suggests that there may be important differences between sexes and that additional research should be conducted to determine whether the cutoffs found here hold for both males and females and across age

groups. We also highlight some problems with the questionnaire and therefore suggest the importance of revisiting its layout to reduce the number of missing subscores and error in the distance subscore.

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Appendix A

Ethics Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING
HOSPITALS RESEARCH ETHICS BOARD



March 21, 2011

This Ethics Application was subject to:

- Full Board Review
Meeting Date:
 Expedited Review

Mr. Stephen Sagar
Department of Community Health and Epidemiology
c/o KGH Clinical Research Centre
Angada 5-315
Kingston General Hospital

Dear Mr. Sagar,

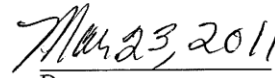
Study Title: Validation of the Walking Impairment Questionnaire for evaluation of the severity of intermittent claudication pain among patients with peripheral arterial disease
Co-Investigators: Dr. Joan Tranmer, Dr. Peter Brown, Dr. William Pickett, Dr. David Zelt, Dr. Ann Brown, Dr. Robert Ross

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following list of ethics requirements you must fulfill over the course of your study:

- **Reporting of Amendments:** If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. (see <http://www.queensu.ca/vpr/reb.htm>).
- **Reporting of Serious Adverse Events:** Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information.
- **Reporting of Complaints:** Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. **Note:** All documents supplied to participants must have the contact information for the Research Ethics Board.
- **Annual Renewal:** Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,


Chair, Research Ethics Board


Date

ORIGINAL TO INVESTIGATOR - COPY TO DEPARTMENT HEAD - COPY TO HOSPITAL - BINDER COPY - FILE COPY

Study Code: EPID-342-11

- **Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete**

**QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING
HOSPITALS RESEARCH ETHICS BOARD**



The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards as defined by the Tri-Council Policy Statement; Part C Division 5 of the Food and Drug Regulations, OHRP, and U.S DHHS Code of Federal Regulations Title 45, Part 46 and carries out its functions in a manner consistent with Good Clinical Practices.

Federalwide Assurance Number : #FWA00004184
#IRB00001173

**Current 2011 membership of the Queen's University Health Sciences
& Affiliated Teaching Hospitals Research Ethics Board**

Dr. A.F. Clark	Emeritus Professor, Department of Biochemistry, Faculty of Health Sciences, Queen's University (Chair)
Dr. H. Abdollah	Professor, Department of Medicine, Queen's University
Dr. R. Brison	Professor, Department of Emergency Medicine, Queen's University
Dr. M. Evans	Community Member
Dr. S. Horgan	Manager, Program Evaluation & Health Services Development, Geriatric Psychiatry Service, Providence Care, Mental Health Services Assistant Professor, Department of Psychiatry
Ms. D. Morales	Community Member
Dr. W. Racz	Emeritus Professor, Department of Pharmacology & Toxicology, Queen's
Dr. B. Simchison	Assistant Professor, Department of Anesthesiology, Queen's University
Dr. A.N. Singh	WHO Professor in Psychosomatic Medicine and Psychopharmacology Professor of Psychiatry and Pharmacology Chair and Head, Division of Psychopharmacology, Queen's University Director & Chief of Psychiatry, Academic Unit, Quinte Health Care, Belleville General Hospital
Dr. E. Tsai	Associate Professor, Department of Paediatrics and Office of Bioethics, Queen's University
Rev. J. Warren	Community Member
Ms. K. Weisbaum	LL.B. and Adjunct Instructor, Department of Family Medicine (Bioethics)

Appendix B

Example scoring of the WIQ

How difficult was it for you to:	Weight	Example answer	Example Likert score
Distance			
Walk indoors such as around our home?	20	No difficulty	4
Walk 50 feet?	50	No difficulty	4
Walk 150feet?	150	Slight difficulty	3
Walk 300 feet?	300	Some difficulty	2
Walk 600feet?	600	Some difficulty	2
Walk 900 feet?	900	Much difficulty	1
Walk 1500feet?	1500	Unable to do	0
Speed			
Walk 1 block slowly?	1.5	Some difficulty	3
Walk 1 block average speed	2	Slight difficulty	2
Walk 1 block quickly?	3	missing	missing
Run of jog 1 block?	5	Unable to do	0
Stair climbing ability			
Climb 1 flight of stairs?	1	Some difficulty	3
Climb 2 flights of stairs?	2	missing	missing
Climb 3 flights of stairs?	3	Unable to do for other reason	missing

$$\text{Distance score} = \frac{4 \times 20 + 4 \times 50 + 3 \times 150 + 2 \times 300 + 2 \times 600 + 1 \times 900 + 0 \times 1500}{4 \times 20 + 4 \times 50 + 4 \times 150 + 4 \times 300 + 4 \times 600 + 4 \times 900 + 4 \times 1500} \times 100 = \frac{3430 \times 100}{14080} = 24.4$$

$$\text{Speed score} = \frac{3 \times 1.5 + 2 \times 2 + 0 \times 5}{4 \times 1.5 + 4 \times 2 + 4 \times 5} \times 100 = \frac{8.5}{35} \times 100 = 25.0$$

(note: weight of 3 removed from denominator as answer missing)

Stair score : more than half the items are missing or unable to do for other reason so score is missing

Combined stair and distance : stair score is missing so this combined score is missing

$$\text{Combined speed and distance} = \frac{25.0 + 24.4}{2} = 24.7$$

Combined stair and speed : stair score is missing so this combined score is missing

Overall score : stair score is missing so overall score is missing

Appendix C

Smoking status questions

11. Have you ever smoked a whole cigarette? *(circle only one)*

1	Yes
2	No

12. At the present time, do you smoke cigarettes daily, occasionally or not at all? *(circle only one)*

1	Daily
2	Occasionally
3	Not at all

13. Have you ever smoked cigarettes daily? *(circle only one)*

1	Yes
2	No

14. How many years did you smoke (cigarettes) daily? *(circle only one)*

0	I have never smoked daily
1	Less than one year
2	1 to 2 years
3	3 to 5 years
4	5 to 10 years
5	10 to 20 years
6	More than 20 years

15. How many cigarettes did/do you usually smoke each day?

_____Cigarettes

16. When did you stop smoking?

(circle only one)

1	I have never smoked
2	I am a current smoker
3	Less than one year ago
4	1 to 2 years ago
5	3 to 5 years ago
6	More than 5 years ago

Appendix D

Metric-Imperial conversion

In this thesis most values were reported in imperial units as the treadmill protocol and the WIQ were both in imperial units. Here are some of the important values converted to metric.

measure	imperial	metric
Initial treadmill speed	1.1 mph	1.8 Km/h
Speed increase increments	0.1 mph	0.16 Km/h
Maximum treadmill speed	2 mph	3.2 Km/h
Minimum treadmill distance	0.03 miles	0.05 Km
Maximum treadmill distance	0.98 miles	1.58 Km
WIQ distance	20 feet	6.1 m
WIQ distance	50 feet	15.2 m
WIQ distance	150 feet	45.7 m
WIQ distance	300 feet	91.4m
WIQ distance	600 feet	182.9 m
WIQ distance	900 feet	274.3 m
WIQ distance	1500 feet	457.2 m
WIQ speed	1.5 mph	2.4 Km/h
WIQ speed	2 mph	3.2 Km/h
WIQ speed	3 mph	4.8 Km/h
WIQ speed	5 mph	8.0 Km/h