IHE Report

Exercise Testing for the Prediction of Cardiac Events in Patients with Diabetes

May 2009

IHE
INSTITUTE OF HEALTH ECONOMICS
ALBERTA CANADA

IHE Board of Directors

HTA Full Report

Exercise Testing for the Prediction of Cardiac Events in Patients with Diabetes

Bing Guo
Christa Harstall

Acknowledgements

The Institute of Health Economics is most grateful to the following individuals for review and provision of information and comments on the draft report. The views expressed in the final report are those of the Institute.

- Dr. Timothy Church, John S. McIlhenny Endowed Chair in Health Wisdom, Pennington Biomedical Research Center, Louisiana State University System, Louisiana, United States
- Dr. William A. Dafoe, Associate Professor of Medicine, Division of Cardiology, University of Alberta, Alberta, Canada
- Prof. Jenny Doust, Professor of Public Health, Faculty of Health Sciences and Medicine, Bond University, Queensland, Australia
- Dr. Ronald J. Sigal, Associate Professor of Medicine, Department of Medicine, Division of Endocrinology and Metabolism, University of Calgary, Alberta, Canada

The authors also wish to thank the following individuals for providing information regarding the local context:

- Ms. Cindy Colbourne, Chronic Disease Clinical Lead, Alberta Health Services – Jasper to Cold Lake (previously Aspen Health Region), Alberta, Canada
- Mr. Greg Cutforth, Physical Therapy Clinical Lead, Alberta Health Services – Jasper to Cold Lake (previously Aspen Health Region), Alberta, Canada
- Ms. Gwenda Davies, Administrative Assistant, Living Well Program, Chronic Disease Programs Network, Alberta Health Services – Central Zone (previously David Thompson Health Region), Alberta, Canada
- Ms. Angela Fulton, Regional Chronic Disease Programs Manager, Alberta Health Services – Central Zone (previously David Thompson Health Region), Alberta, Canada

Support from IHE Staff

The literature search for the review was undertaken by Patricia Chatterley, Information Specialist, Institute of Health Economics and University of Alberta, Edmonton, Canada.

Maria Ospina, Research Associate, Institute of Health Economics, assisted with the methodological quality assessment of the selected studies.

Competing interest

The author(s) of this report declared no competing interest.

All external reviewers are asked to sign a declaration of competing interest.

Competing interest is considered to be financial interest or non-financial interest, either direct or indirect, that would affect the research contained in this report or create a situation in which a person's judgment could be unduly influenced by a secondary interest such as personal advancement.

On the basis of the statement above, the external reviewers declared no competing interest.

Production of this document has been made possible by a financial contribution from Alberta Health and Wellness. The views expressed herein do not necessarily represent the official policy of Alberta Health and Wellness.

EXECUTIVE SUMMARY

Background

Chronic diseases such as diabetes are a significant public health problem in Canada and worldwide. Patients with diabetes have a higher risk of developing cardiovascular disease, which is the leading cause of death in this population. Physical exercise is a key component of the clinical management of diabetes. Clinical practice guidelines based on expert consensus recommended that exercise testing be performed for sedentary patients with diabetes before they start a more vigorous exercise. However, exercise testing is not widely available in some rural areas in Alberta, Canada, which poses a significant barrier for patients with diabetes to participate in community-based supervised exercise programs.

Objectives

To assess research evidence on the safety and prognostic value of exercise testing for the prediction of cardiac events in patients with chronic diseases including diabetes, chronic obstructive pulmonary disease (COPD), and arthritis.

Results

No systematic reviews or primary studies on COPD and arthritis that met the inclusion criteria were located through a comprehensive literature search.

Five primary prognostic studies with eight publications examined the association of prognostic variables derived from exercise electrocardiogram (ECG) tests or cardiopulmonary exercise tests and the number of cardiac events that occurred in patients with diabetes over a 2.8 to 16 year period.

The majority of the patients included in these studies had no history of cardiovascular disease or symptoms of coronary heart disease such as chest pain; however, they differed in terms of types, duration, and presence of secondary complications of diabetes, as well as co-morbidities such as hypertension. Four studies used the exercise ECG test and examined prognostic variables such as ECG ST-segment depression, Duke Treadmill Score, heart rate recovery, chronotropic responses, and metabolic equivalents. One study used the cardiopulmonary exercise test and examined the prognostic variable peak oxygen uptake. No study considered physician judgment as a prognostic variable; however, all studies included body mass index, blood pressure, and resting heart rate as covariates. Clinical outcomes measured in these studies included cardiovascular mortality and/or non-fatal cardiac events such as myocardial infarction.

These studies demonstrated that prognostic variables, including ECG ST-segment depression, low Duke Treadmill Score, delayed heart rate recovery, impaired chronotropic responses, reduced metabolic equivalents, and low peak oxygen uptake, are independent and significant predictors of cardiovascular mortality and non-fatal cardiac events.

However, the prognostic value of these tests might be overestimated because of potential publication bias; that is, only studies with positive results might have been published. Moreover, no conclusion could be drawn in terms of the prognostic value of exercise testing in patients with COPD or arthritis because of the lack of sufficient published evidence.

Conclusions

The published evidence indicates that the exercise ECG test and the cardiopulmonary exercise test can provide important prognostic information for future cardiac events in patients with diabetes. However, there is a lack of research evidence currently available that examined the incremental prognostic value of exercise testing compared with physicians' judgment based on medical history and physical examination.

Patients with diabetes, who often have silent myocardial ischemia, may be at risk of future cardiac events when participating in a more vigorous exercise program than brisk walking if they are previously physically inactive. Therefore, exercise testing may provide additional prognostic information for those patients with diabetes planning to enter a structured community-based exercise program although there is a lack of direct research evidence.

Method

This is a qualitative systematic review. A comprehensive literature search was conducted to identify research articles published from 1997 to 2009. Electronic databases searched included the Cochrane Library; Centre for Reviews and Dissemination (CRD) Databases: Databases of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) and the National Health Services Economic Evaluation Database (NHS EED); MEDLINE; EMBASE; Web of Science; PEDro; and SPORTDiscus. Clinical practice guidelines, websites of various HTA agencies, and reference lists of retrieved articles were also searched.

The critical appraisal of the quality of the research evidence was conducted using a 10-item checklist. Two researchers independently applied the quality assessment checklist. Disagreements were resolved by discussion and consensus.

Reference: Guo B, Harstall C. *Exercise testing for the prediction of cardiac events in patients with diabetes*. Institute of Health Economics, Edmonton AB: May 2009, HTA Full Report.

ABBREVIATIONS

ACSM	American College of Sports Medicine
ABI	ankle brachial index
ADA	American Diabetes Association
AER	albumin excretion rate
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CAD	coronary artery disease
CHD	coronary heart disease
CHF	chronic heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise testing
CR	chronotropic response
CV	cardiovascular
CVA	cerebrovascular accident
CVD	cardiovascular disease
DTS	Duke Treadmill Score
ECG	electrocardiogram
EOB	exercise oscillatory breathing
HR	hazard ratio
HRR	heart rate recovery
MACE	major adverse cardiac events
METs	metabolic equivalents
MI	myocardial infarction
mph	miles per hour
6MWT	6-minute walking test
RER	respiratory exchange ratio
SMI	silent myocardial ischemia
SpO_2	pulse oximetry
VCO_2	carbon dioxide output
VE	minute ventilation
VO_2	oxygen uptake
VE/VCO_2	rate of increase in ventilation per unit increase in carbon dioxide production

GLOSSARY OF TERMS

Main source: Tremblay et al. 2007[1] Sigal et al. 2004[2]

Cardiorespiratory fitness – also known as cardiorespiratory endurance or aerobic fitness. It is the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity.

Electrocardiogram – a test that records the electrical activity of the heart. Information about heart rate, rhythm, and electrical conduction is recorded. Evidence of damage, ischemia, and hypertrophy can be identified.

Exercise prescription – the process whereby a person's recommended regimen of physical activity is designed in a systematic and individualized manner.

Exercise intolerance – an inability to complete a required physical task successfully.

Maximal VO_2 – the point at which no further increase in measured VO_2 occurs despite an increase in work rate (a plateau is reached) during graded exercise testing. It is defined as the greatest rate at which oxygen can be consumed during exercise or the maximal rate at which oxygen can be taken up, distributed, and used by the body during physical activity.

Metabolic equivalent (MET) – a measure of energy output equal to the basal metabolic rate of a resting, seated, awake individual. One MET equals the resting metabolic rate of approximately 3.5 mL O_2 per kilogram of body weight per minute. Formula: $(1.44 \times [\text{maximal minutes on treadmill}] + 14.99)/3.5$. Physical activity intensity is often expressed in multiples of METs.

Peak VO_2 – the highest VO_2 attained during graded exercise testing, but the term does not imply that a plateau in measured VO_2 is reached.

Physical activity – any body movement produced by the contraction of skeletal muscles that result in a substantial increase over resting energy expenditure.

Physical fitness – a physiological state of well-being that enables the individual to meet the demands of daily living and/or provide the basis for sport performance. It includes cardiorespiratory fitness, muscular fitness, and flexibility.

Silent myocardial ischemia (SMI) – objective documentation of myocardial ischemia in the absence of angina or angina equivalents.

TABLE OF CONTENTS

List of Tables and Figures

Introduction

This report was prepared in response to a request from two rural health regions in Alberta, Canada: the David Thompson and Aspen Health Regions. The two health regions have implemented community-based supervised exercise programs for people with chronic diseases. Although until recently only a physician's judgment based on medical history and physical examination was required for pre-participation screening of patients' cardiac risk, exercise testing is now recommended according to recent clinical practice guidelines. However, lack of local access to exercise testing within some rural communities poses a significant barrier for patients to participate in exercise programs. The exercise program managers found that recommendations from the clinical practice guidelines tend to rely on expert consensus and that primary research results appeared to conflict. This issue led to a question about the state of the evidence concerning exercise testing as a predictor of cardiac risk, in addition to physician's judgment, in patients with chronic diseases prior to participating in a community-based exercise program.

Scope of the Report

Addressing this practical issue appeared to be complex as it involved various patient groups with different chronic diseases, different types of exercise testing, and different outcome measures. Through several meetings with the regional health managers the following was agreed to based on the PICO (population, intervention, comparator, outcomes) model:

Population: patients with diabetes (type 1 or type 2), chronic obstructive pulmonary disease (COPD), or arthritis.

Intervention: exercise tests of interest, including exercise electrocardiogram (ECG) test, cardiopulmonary exercise test (CPET), and 6-minute walking test (6MWT). Pharmacological stress tests and the use of imaging technologies (e.g. radionuclide imaging, echocardiography) were excluded.

Comparator: physician's judgment based on medical history and physical examination.

Outcome measures: safety of performing exercise testing and prognostic value of exercise testing in predicting cardiac events during exercise.

This systematic review focuses on the prognostic value rather than diagnostic value of exercise testing. A comprehensive literature search (see Appendix A: Method/Search strategy) did not locate any primary prognostic studies on patients with COPD or arthritis that met the pre-defined inclusion criteria (see Appendix A: Method/Study selection); therefore, this report focused solely on patients with diabetes.

Background

Clinical condition

Definition

Diabetes mellitus is a chronic metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action, or both.[3] Type 1 diabetes is primarily a result of pancreatic beta cell destruction caused by an autoimmune process or unknown mechanisms. Type 2 diabetes results from a progressive insulin secretory defect on the background of insulin resistance.[4]

Epidemiology

Diabetes is currently one of the most common non-communicable diseases globally and is quickly emerging as one of the most serious public health problems.[5] It was estimated that 246 million people worldwide had diabetes in 2007, representing 5.9% of the adult population (age 20 to 79 years).[5] Diabetes is the fourth leading cause of death by disease globally,[5] and approximately 3.8 million adults die from diabetes-related causes each year.[5] Furthermore, type 2 diabetes, a disease that often affects older people, has increased substantially in younger people. It is also increasing in children as well as in adolescents as a consequence of increased obesity among young people. Worldwide, the 40- to 59-year age group currently has the greatest number of persons with diabetes.[5]

Currently more than two million Canadians have diabetes.[6] Type 2 diabetes accounts for about 90% of all diagnosed cases, with over 60,000 new cases each year.[6] In Alberta, 130,000 adults are living with diabetes, and 12,000 new cases of diabetes were identified in 2004.[7]

Prognosis

Chronic hyperglycemia (i.e. increased blood sugar levels) is associated with significant long-term complications involving various organs, particularly the kidneys, eyes, nerves, heart, and blood vessels.[3] The mechanisms by which diabetes leads to secondary complications are complex. They are not fully understood but are directly related to the toxic effects of high glucose levels, along with the impact of elevated blood pressure, abnormal lipid levels, and both functional and structural abnormalities of small blood vessels.[8]

Patients with diabetes are 2 to 4 times more likely to develop cardiovascular diseases than the general population.[8] Approximately 65% to 75% of patients with diabetes die of cardiovascular disease.[9]

Furthermore, coronary artery disease in patients with diabetes is often silent, more advanced and diffuse, and associated with less favourable prognoses than those in the non-diabetic population.[10]

Silent myocardial ischemia (SMI) is defined as objective documentation of myocardial ischemia (e.g. detected by exercise testing) in the absence of symptoms (e.g. chest pain) due to differences in pain threshold sensitivity and autonomic neuropathy.[11,12] Studies have demonstrated that a significant percentage of patients with diabetes who have no symptoms of coronary artery disease have abnormal stress tests.[10] Patients with diabetes may remain asymptomatic until immediately before an acute major cardiac event.[10] In approximately 50% of patients, the first manifestation of silent coronary artery disease is a fatal cardiac event.[13]

Diabetes is the most common cause of kidney failure in developed countries.[5] Microalbuminuria, defined as a urinary albumin excretion rate between 20 and 200 µg/minute, is present in approximately 25% of patients with type 2 diabetes and is associated with a doubling of the risk of early death, mainly from coronary heart disease.[14]

Management – physical exercise

Regular physical exercise is a key part of the treatment plan for patients with diabetes.[3] Exercise can help achieve a variety of goals, including improved control of blood glucose, increased insulin sensitivity, improved blood lipoprotein profile and lowered blood pressure, increased vigour, and improved cardiovascular and muscular fitness. It is useful as an adjunct to diet for weight reduction, enhanced sense of well-being and quality of life, and reduced risk of heart disease and stroke.[3,15]

Studies have demonstrated that moderate to high levels of physical activity and cardiorespiratory fitness are associated with substantial reductions in morbidity and mortality in both men and women with either type 1 or type 2 diabetes.[3] However, a Canadian study showed that 63.7% of 682 patients with type 1 diabetes and 71.9% of 1593 patients with type 2 diabetes were not achieving recommended physical activity level, defined as achieving ≥ 600 MET minutes per week of moderate and/or vigorous activity.[16] A US study[17] also indicated that only 38.5% to 41.7% of patients with diabetes met the American Diabetes Association recommendations for aerobic physical activity (≥150 minutes a week of moderate-intensity physical activity or at least 90 minutes a week of vigorous aerobic exercise).[4]

Safety concerns about exercise

Starting an exercise program or increasing one's level of physical exercise means a transient increased risk of negative health outcomes, ranging from joint problems to sudden cardiac death.[18] Cardiac arrest is more likely to occur during exercise than at rest, and this association is much stronger in sedentary than in active persons.[19] Studies have shown that the risk of acute myocardial infarction during or immediately after strenuous physical exertion was 2 to 6 times greater than the risk during periods of lighter activity or rest in people with or without known coronary heart disease.[20] Furthermore, 10% of heart attacks occur during or immediately after vigorous exertion, making vigorous exertion one of the most common triggers of acute heart attack.[21]

Pathologic evidence suggests that increased myocardial demands can precipitate cardiovascular events in patients with documented or occult coronary artery disease. For people with coronary artery disease, the increase in heart rate and blood pressure during intensive exercise may disrupt the deposits in the narrowed coronary blood vessels, setting into motion a chain of events that can cause a complete blockage and heart attack.[15]

Surveys have revealed that 50% of health/fitness facility members are older than 35 years and that the fastest-growing segments are middle-aged and older participants.[15] According to the American Heart Association, a considerable proportion of Americans have some form of cardiovascular disease (including hypertension), and the prevalence rises with age.[15] To ensure safe participation in exercise programs, therefore, it is essential that people with underlying cardiovascular disease be identified before they participate in a vigorous exercise program.[15]

Pre-exercise examinations

The exercise test, a common physiological stress test, can elicit cardiovascular abnormalities that are not present at rest and can be used to determine cardiac function.[22] A number of professional organizations (e.g. American College of Sports Medicine, Australian Association for Exercise and Sports Science) have recommended pre-exercise screening procedures to identify those at particular risk from functional exercise testing and/or from subsequent exercise prescription. These procedures usually involve risk stratification, which categorizes individuals into various classes (known disease, at higher risk, apparently healthy).[18] On the basis of this stratification, decisions are made as to whether the individual needs to undergo a medical screening by a physician, including a stress ECG test and blood tests, and whether a physician needs to be present during maximal or sub-maximal testing.[18]

Overview of Technology – Exercise Testing

Description of exercise testing

Exercise testing is a controlled physical activity, usually performed on a treadmill or stationary bicycle, that is used to assess how well the heart and the body deal with exercise or stress.[23] It is designed to increase total body and myocardial oxygen demands at safe increments within a reasonable time. This requires dynamic exercise that uses major muscle groups, permitting a large increase in cardiac output, oxygen delivery, and gas exchange.[24] When performed appropriately, exercise testing yields valuable diagnostic, prognostic, functional, and therapeutic information at a relatively low cost and with minimal risk.[25]

Among the many types of exercise tests used for prognostic purposes, three exercise tests, the exercise ECG test (or graded exercise test), the cardiopulmonary stress test (CPET), and the 6-minute walking test (6MWT), are of interest in this report. These exercise tests differ in terms of equipment used, monitoring systems, parameters measured, and definitions of positive test results.

Exercise ECG test (graded exercise test)

This test is performed on a bicycle or treadmill and is used primarily for the diagnosis of coronary artery disease (myocardial ischemia) and arrhythmias, and to assess therapeutic interventions. During the test, ECG and blood pressure are monitored.

Protocols suitable for clinical testing consist of an initial low-intensity warm-up phase, 8 to 10 minutes of continuously progressive exercise during which the myocardial oxygen demand is elevated to the patient's maximal level, and a suitable recovery or cool-down period.[22,26] The Bruce protocol, consisting of five progressive stages, each 3 minutes in duration, is the most popular. The metabolic equivalents (METs) increments in the Bruce protocol are large and uneven, which limits the number of sub-maximal responses that may be observed in relation to exercise states. The Balke-Ware protocol is a particularly attractive alternative because of its constant treadmill speed of either 2.0 or 3.3 mph[26] and grade increments of 1% applied every one minute (Dr. R Sigal, personal communication, January 2009). The Ramp protocol, in which work increases constantly and continuously, is a relatively new and very useful protocol.[26]

Interpretation of the exercise ECG test should include exercise capacity and clinical, hemodynamic, and electrocardiographic responses.[19] Variables such as exercise capacity, exercise duration, positive exercise ECG, abnormal change in systolic blood pressure during exercise, marked cardiac arrhythmia, and delayed heart rate recovery are associated with the risk of death and cardiovascular morbidity even among apparently healthy and asymptomatic individuals.[27]

Symptoms during exercise test: The occurrence of ischemic chest pain consistent with angina is important, particularly if it forces termination of the test.

ST-segment deviation: The most important ECG findings are ST-segment depression or elevation, which helps identify underlying cardiovascular disease. The most commonly used definition of a positive result on exercise testing is greater than or equal to 1 mm of horizontal or down-sloping ST-segment depression or elevation for at least 60 to 80 milliseconds after the end of the QRS complex.[19]

Duke Treadmill Score (DTS): The DTS has been recommended by the American College of Cardiology/American Heart Association for cardiac risk stratification.[19] It incorporated three components – exercise duration, ST-segment changes on ECG, and presence of angina – in a simple and quantitative equation that is calculated as:

duration of exercise in minute − (5 × maximal ST deviation

during or after exercise, in mm) − (4 × treadmill angina index)

The treadmill angina index is coded as 0 if no angina, 1 if typical angina occurred during exercise, and 2 if angina is the reason for stopping exercise. Patients with a DTS ≥ 5 were classified as low risk (99% 4-year survival), -10 to 4 as intermediate risk (95% 4-year survival), and < -10 as high risk (79% 4-year survival).[28]

Heart rate recovery (HRR) is the difference between the maximal heart rate during exercise testing and the heart rates 1, 2, or 5 minutes after discontinuation of exercise testing.

Chronotropic response (CR) is the ability to achieve 85% of predicted maximal heart rate during exercise testing (calculated as 220 − age). Impaired chronotropic response is defined as the inability of the heart rate to increase normally with exercise and may be related to alterations in sympathetic and parasympathetic tone as well as to autonomic dysfunction.

Exercise capacity is measured by metabolic equivalents, using the formula:

(1.44 × [maximal minutes on treadmill] + 14.99)/3.5

Cardiopulmonary exercise testing (CPET)

CPET combines the routine measurements of the ECG, blood pressure, and work output with the analysis of exhaled gases, which allows the simultaneous assessment of the cardiovascular and respiratory systems along with the assessment of gas exchange.[29-31]

CPET involves measuring oxygen uptake (VO_2), carbon dioxide output (VCO_2), minute ventilation (VE), and other variables in addition to monitoring ECG, blood pressure, and pulse oximetry (SpO_2) during a maximal symptom-limited incremental exercise test on the cycle ergometer or treadmill.[32] When appropriate, the additional measurement of arterial blood gases provides important information on pulmonary gas exchange.[33] Symptoms such as dyspnea, fatigue, and chest pain are also recorded during the test.

The key measurement is peak oxygen uptake, a measure of physical fitness, whose usefulness as a prognostic marker is widely accepted.[34] Oxygen uptake rises during incremental exercise and peak oxygen uptake represents the highest rate of oxygen uptake achieved on a test performed to the limit of tolerance.[32] A reduction in its level may result from a variety of factors, including limitation in cardiac output, poor peripheral blood flow, impaired skeletal muscle metabolism, or early termination of the test because of cardiac-related or other symptoms. The prognostic significance of peak oxygen uptake may result from its dependence on a clinically relevant combination of these numerous mechanisms of impairment of functional capacity.[34]

The protocols vary in terms of their correlation with peak oxygen uptake. Ramp-type protocols have the highest correlation with peak oxygen uptake, whereas the Bruce protocol has less correlation (Dr. W Dafoe, personal communication, January 2009).

Six-minute walking test (6MWT)

The 6MWT is a practical, simple test that measures the maximal distance that a patient can walk at his/her own pace in 6 minutes.[33] This self-paced test is performed in an indoor corridor. The 6MWT provides a global assessment of functional capacity but does not provide specific information on each of the different organ systems involved in exercise, including mechanisms of exercise limitation.[35] Therefore, this test has limited diagnostic capacity, especially for occult ischemia and combined heart-lung disease.[33]

In clinical practice, the 6MWT is commonly used to assess changes in functional exercise capacity following pulmonary rehabilitation, with the primary outcome reported being the distance walked during the time of the test.[36] Compared to laboratory-based tests using a cycle ergometer or treadmill, these field walking tests have advantages of increased availability and low cost; furthermore, ground-based walking is more representative of activities of daily living than some other tests are.[36]

The 6MWT is primarily useful in very debilitated people. In most younger and middle-aged patients with diabetes it would be inadequate to test their exercise capacity. It also is not useful for detecting myocardial ischemia (Dr. R Sigal, personal communication, January 2009).

Indications and contraindications

Indications

In patients with diabetes who plan to start a vigorous exercise program, exercise testing may be helpful both for the screening of silent coronary artery disease and for exercise prescription.[13]

A key issue facing clinicians is to risk-stratify the long-term likelihood of morbidity and mortality due to coronary artery disease and to identify those patients who might benefit from more aggressive treatment strategies to mitigate these risks.[9]

According to a review article, no evidence suggests that patients who initiate physical activity by walking or similar exercise increase their risk of a cardiovascular disease event; therefore, these patients are unlikely to need a stress test.[10] Exercise stress testing is indicated for patients who will be exercising beyond their level of daily living activities, or those who are at increased mortality risk.[10]

Contraindications

Absolute and relative contraindications to exercise ECG testing according to the American College of Cardiology/American Heart Association guidelines for exercise testing are summarized in Table 1.

Table 1: Contraindications to exercise testing

Absolute
- Acute myocardial infarction (within 2 days)
- High-risk unstable angina
- Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
- Symptomatic severe aortic stenosis
- Uncontrolled symptomatic heart failure
- Acute pulmonary embolus or pulmonary infarction
- Acute myocarditis or pericarditis
Relative
- Left main coronary stenosis
- Moderate stenotic valvular heart disease
- Electrolyte abnormalities
- Severe arterial hypertension
- Tachyarrhythmias or bradyarrhythmias
- Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
- Mental or physical impairment leading to inability to exercise adequately
- High-degree atrioventricular block

Source: Gibbons et al. 2002[19]

Safety issues

Although exercise testing is generally considered a safe procedure, both myocardial infarction and death have been reported.[19] A US survey showed that, of a total of 75,828 exercise tests performed during a one-year period, four major cardiac events were reported (three myocardial infarctions and one sustained ventricular tachycardia), representing an event rate of 1.2 per 10,000.[37] Good clinical judgment should therefore be used in deciding which patients should undergo exercise testing and whether a physician's on-site supervision is needed.

Local Context

The Calgary Health Region is a large, primarily urban region in Alberta. It started the *Living Well with a Chronic Condition* program several years ago, and thousands of patients have completed it. We will refer to this as the "Living Well" program. The Aspen and David Thompson Health Regions are rural regions and both have implemented community-based exercise programs throughout their regions based on the Calgary program for patients with a variety of chronic diseases (Dr. R Sigal, personal communication, January 2009).

Since the Aspen Health Region introduced the Living Well exercise program, 146 participants between the ages of 21 and 85 years (mean age 65) with a variety of primary diagnoses such as hypertension (24 patients), coronary artery disease (17 patients), arthritis (17 patients), obesity (13 patients), diabetes (10 patients), and COPD (2 patients) have been enrolled in it. The method used for exercise test triage is presented in Appendix B: Figure 1.

The David Thompson Health Region's Community Care – Chronic Disease Programs Network – Supervised Exercise program has enrolled 67 participants (as of November 2008), including 24 patients with diabetes and 36 with COPD.

According to the chronic disease program managers in the two health regions, using exercise ECG testing is a new requirement for the community-based exercise programs. In the past, only physicians' judgments about patients' safety, based on the medical history and physical examination, were required. The only other screening test is the use of a questionnaire called "PAR-Q (Physical Activity Readiness Questionnaire)" but all patients failed this test (no details were available in terms of specific items that led to exclusion). Lack of availability of exercise ECG testing in local communities, the cost of the test, and lack of human resources present significant barriers to accessing the community-based exercise programs.

Methods of Analyzing Prognostic Studies

Definitions

In this report, *prognostic studies* refer to clinical studies of variables that are predictive of future cardiac events. Variables that are predictive of future events are called independent variables (or prognostic variables), whereas the defined clinical outcomes or endpoints (e.g. cardiac death) are called dependent variables (or target variables).

Independent variables and dependent variables can be continuous or dichotomous. Continuous data such as height, weight, or blood pressure can take on any value in a continuum.[38] Dichotomous data are nominal data that can be divided into two categories, such as yes/no, present/absent, or alive/dead.[38] It is important to select appropriate methods of analyses for different variables in prognostic studies.

Clinical outcomes of prognostic studies are the number of events that occur over time and are expressed in absolute terms (e.g. 5-year survival rate), relative terms (e.g. risk from prognostic variable), or survival curves (cumulative events over time).[39]

Analytical methods and interpretation

Two types of analyses, univariate analysis and multivariate analysis, can be used to examine the relationship between independent variables and dependent variables. Univariate analysis considers only one independent variable at a time, whereas multivariate analysis considers several independent variables at the same time.[40]

As the majority of clinical outcomes (e.g. death) are the results of many variables acting together in complex ways, prognostic studies generally require some sort of multiple regression analysis.[38,41] For outcomes that are dichotomous or time to a specific event, logistic regression or Cox proportional hazards regression models, respectively, are appropriate for examining the influence of several prognostic factors simultaneously.[41]

An exploratory univariate analysis is undertaken first, and then the variables with statistical significance are entered into the multivariate analysis to avoid including too many prognostic factors.[42] Some prognostic factors are only significant when using univariate analysis, but lose significance in a multivariate analysis. This means that the prognostic factor is probably a surrogate for (i.e. highly correlated with) one of the other variables causing the outcome.[42] Multivariate analysis should take precedence over any of the univariate analyses.

The Cox proportional hazards model, which compares two or more categories and measures the hazard ratio (HR) with a 95% confidence interval, is the most common form of analysis for prognostic studies. Hazard is the probability of the clinical endpoint such as death. A HR is the relative effect of a predictive factor on an outcome. HR expresses the effect of each predictive variable included in the Cox model in relation to the reference group, adjusted for other variables in the model. HRs are a comparison of the incidence of the outcome of interest (e.g. death) in two different categories of patients and can be interpreted as a measure of the relative risk. An HR of 1 indicates no difference in the incidence of the outcome of interest between the two patient categories. On the other hand, an HR less than 1 indicates that the incidence of the outcome of interest in a given patient category is lower than that in the reference category.

Available Evidence

Description of the selected studies

A comprehensive and systematic literature search (Appendix A: Method/Search strategy) resulted in the identification of 4414 citations. After the researchers screened titles and abstracts, they retrieved the full texts of 56 potentially relevant articles and evaluated them for inclusion in the report. On closer examination of the full text of the articles, eight published articles met the inclusion criteria (Appendix A: Method/Study selection); the 48 excluded primary studies and the reasons for their exclusion are listed in Appendix C. The search did not locate any relevant systematic reviews on the topic that met Cook's criteria[43] (Appendix A: Method/Study selection).

Of the eight included articles[14,44-50], three were identified as multiple publications of the original study, which were not considered to be unique studies. In total, then, five unique studies with eight articles[14,44-50] were included in this report (Table 2).

Table 2: Overview of the included prognostic studies

Study	No. of patients	Exercise test	Prognostic variable	Follow-up† (year)	Cardiac events
Rutter et al. 2002[14] United Kingdom	86	Exercise ECG test	ST-segment depression	Median 2.8	Sudden cardiac death, AMI, new-onset angina
Lakkireddy et al. 2005[44] United States	100	Exercise ECG test	Duke Treadmill Score	Median 6.6	Cardiac death, non-fatal MI
Cheng et al. 2003[46] United States	2333	Exercise ECG test	Heart rate recovery	Median 14.9	CVD mortality
Church 2005[45]*	2316	Exercise ECG test	Maximal METs	15.9 ± 7.9	CVD mortality
Lyerly et al. 2008[47]*	2854	Exercise ECG test	ECG ST-segment deviation	15.8 ± 9.6	CVD mortality, CHD mortality
Seyoum 2006[48] United States	68	CPET	Peak VO_2	5	Cardiac events
Chacka et al. 200849*	871	Exercise ECG test	Heart rate recovery	5	CVD mortality, non-fatal MI, CHF hospital admission
Ho et al. 2008[50] United States	1,341	Exercise ECG test	Chronotropic response to exercise ECG test	Up to 4.6	MI, revascularization procedures

* Later publications including the patients from a previous study

† Data expressed as mean ± standard deviation unless otherwise indicated

Abbreviations: AMI: acute myocardial infarction; CHD: coronary heart disease; CHF: chronic heart failure; CPET: cardiopulmonary exercise test; CVD: cardiovascular disease; ECG: electrocardiogram; METs: metabolic equivalents; MI: myocardial infarction; No.: number; VO_2: oxygen uptake.

Methodological quality of the selected studies

Two researchers (BG and MS) independently assessed the methodological quality of each of the eight articles. There are no generally accepted or widely used quality assessment tools for prognostic studies. The researchers developed a quality assessment checklist by incorporating some important aspects of a prognostic study proposed by other authors.[41,51,52] This checklist consists of 10 questions within six domains: study design, participants, prognostic factor measurement, follow-up, outcome measurement, and methods of analysis. The checklist and the quality assessment results are summarized in Appendix D.

All but one article scored 'yes' to at least 7 of the 10 questions, indicating an overall acceptable quality of the included articles. All clearly defined methods for measuring prognostic factors, had a complete follow-up (more than 80% of participants completed follow-up), and considered other important prognostic factors in their statistical analysis. Continuous prognostic variables were analyzed appropriately in the majority of the selected studies. However, important information on the study participants were not consistently reported. For example, patient inclusion and exclusion criteria were clearly defined and patients were recruited at a common point in their disease in only two studies. In some studies, it was difficult to determine whether the patients were assembled at a common point in their disease course due to the lack of published information. Two of the five studies followed patients for less than five years, which might have not allowed sufficient time for cardiac events to occur. Furthermore, clinical outcomes of interest were not clearly defined in more than half of the studies. These methodological limitations have an influence on the interpretations of the study results.

Prognostic value of exercise testing

Details regarding the objectives, patient characteristics, exercise tests used, length and rate of follow-up, and outcomes extracted from each of the five studies are presented in Appendix E. Covariates that were considered in these studies are listed in Appendix F.

Five cohort studies (one[46] with two additional publications[45,47] and one[48] with one additional publication[49]) examined prognostic values of variables measured during exercise testing for predicting future cardiac events among patients with type 1 or type 2 diabetes (Table 3). Four studies were conducted in the United States, whereas one[14] was conducted in the United Kingdom. The total number of participants included in these studies ranged from 86 to 2854, with mean ages ranging from 49 to 62 years. The study[46] with two additional publications[45,47] had the largest sample size (more than 2000), but included only male participants with a wide variation in age (range from 21 to 99 years). In addition, information on the duration of diabetes was not available in this study.

Table 3: Characteristics of the included participants

Study	Total number	Age (years)*	Gender (M/F)	BMI (kg/m2)*	Duration of DM (years)*
Rutter et al.[14]	86	62 ± 7 (range 46 to 74)	62/24	29.8 ± 5.0	Median 7 (range 1 to 23)
Lakkireddy et al.[44]	100	59 ± 10	58/42	31 ± 6	NA
Cheng et al.[46]	2333	49.4 ± 9.5 (range 23 to 79)	2333/0	27.5	NA
Church et al.[45]	2316	50 ± 10 (range 21 to 99)	2316/0	26.8 ± 3.4	NA
Lyerly et al.[47]	2854	49.5 ± 9.7	2854/0	28	NA
Seyoum et al.[48]	468	57.6	307/161	31.2	9.1
Chacko et al.[49]	871	58.5 ± 8.2	549/322	31.4 ± 5.5	8.8 ± 7.0
Ho et al.[50]	1341	NA	NA	NA	NA

*Data are mean ± standard deviation or mean unless otherwise indicated

Abbreviations: BMI: body mass index; DM: diabetes; F: female; kg: kilogram; M: male; m: metre; NA: not available.

As shown in Table 4, the treadmill exercise ECG test was used in four studies and CPET was used in one study.[48] The primary prognostic variables under investigation varied across the studies; they included ECG ST-segment depression (two studies), the Duke Treadmill Score (one study), exercise capacity measured by peak VO_2 (one study), cardiorespiratory fitness measured by METs (one study), and heart rate recovery following exercise (two studies), and impaired chronotropic response to exercise test (one study). The follow-up periods were sufficiently long (defined as longer than 5 years) for all but one study.[14] In four studies, outcomes were measured blinded to the status of the prognostic variables; however, this information is not provided in one study.[50]

Table 4: Prognostic variables under investigation

Study	Prognostic variable	Follow-up (year)	Blinded outcome measurement	Frequency of cardiac events	Independent predictor
Rutter et al.[14]	ECG ST-segment depression	Median 2.8 (range 1.3 to 4.9)	Yes	23 events in 15 patients (17%): Sudden cardiac death: 3 AMI: 7 events New-onset angina: 13 events	Silent myocardial ischemia Ankle brachial index
Lakkireddy et al.[44]	Duke Treadmill Score (DTS)	Median 6.6	Yes	Cardiac death or MI: 8 patients (8%) Revascularization and CHF: 39 patients (39%)	DTS
Cheng et al.[46]	Heart rate recovery (HRR)	Median 14.9 (range 1 to 25)	Yes	CVD mortality: 142 patients (6.1%)	Delayed HRR
Church et al.[45]	Maximal METs	Mean (SD) 15.9 ± 7.9	Yes	CVD mortality: 179 patients (7.7%)	Maximal METs, fasting glucose level, systolic BP, parental history of premature CVD, abnormal exercise ECG (ST-depression)
Lyerly et al.[47]	ECG ST-segment deviation	Mean (SD) 15.8 ± 9.7	Yes	CVD mortality: 210 patients (7.4%) CHD mortality: 133 patients (4.7%)	Equivocal and abnormal exercise ECG test, BMI ≥ 30, hypertension, hypercholesterolemia
Seyoum et al.[48]	Peak VO_2	5	Yes	CVD events (cardiac death, non-fatal MI, non-fatal cerebral vascular accident, CHF requiring hospital admission, pulmonary infarction): 71 patients (15.2%)	Peak VO_2, duration of diabetes, overt albuminuria
Chacko et al.[49]	HRR	5	Yes	CV mortality: 35 patients (4.0%) CV events (non-fatal MI, CVA, and CHF requiring hospital admission): 135 (15.5%)	Delayed HRR, urinary albumin excretion, macro-vascular complications
Ho et al.[50]	CR	Up to 4.6	NA	MI: 31 patients (2.3%)	Impaired CR

Abbreviations: CHD: coronary heart disease; CHF: chronic heart failure; CR: chronotropic response; CV: cardiovascular; CVA: cerebrovascular accident; CVD: cardiovascular disease; DTS: Duke Treadmill Score; ECG: electrocardiogram; HRR: heart rate recovery; METs: metabolic equivalents; MI: myocardial infarction; SD: standard deviation; VO_2: oxygen uptake

ECG ST-segment deviation

One study[14] examined the prognostic value of silent myocardial ischemia (SMI) (defined as exercise-induced ST-segment depression in the absence of coronary heart disease symptoms such as angina) and microalbuminuria in predicting cardiac events in 86 asymptomatic patients with type 2 diabetes free from known coronary heart disease; 43 patients had microalbuminuria at baseline. This study did not provide details of the diagnostic criteria, and the participants differed at baseline in terms of the secondary complications of diabetes such as peripheral neuropathy or retinopathy. Furthermore, the follow-up period in this study was relatively short (less than 5 years).

Of the 86 patients, 45 (52%) were found to have SMI. The study suggested that SMI was more strongly related to the presence of cardiac events than the presence of microalbuminuria. Patients with both SMI and microalbuminuria were much more likely to experience cardiac events compared to other patients.

The study found that the only independent predictive variables were SMI and ankle brachial index (ABI: ratio of ankle and brachial systolic blood pressure). It also found that SMI was the single most sensitive test for the identification of patients at risk for developing coronary heart disease events.

This study showed that the presence of SMI assessed by exercise ECG was strongly and independently related to subsequent cardiac events in asymptomatic patients with type 2 diabetes and had good sensitivity (100%) and negative predictive value (100%). The relationship of SMI to cardiac events is independent of the presence of microalbuminuria.

It is of note that the high prevalence of SMI and the high event rate in this study is probably explained by the selection of only type 2 diabetes, the age of the patients (mean age 62 years), the high proportion (50%) of patients with microalbuminuria, and the geographical area, which has a high prevalence of coronary heart disease. The high sensitivity of treadmill exercise testing in this study is probably explained by patient selection (older and high proportion with microalbuminuria), a population at high risk. The high incidence of cardiac events in this study's population increases the positive predictive value of the test.

A US study[47] also examined the relationship between abnormal ECG tests and coronary heart disease (CHD) mortality and cardiovascular disease (CVD) mortality. This article is one of the multiple publications of the Aerobics Center Longitudinal Study, an ongoing epidemiology study. The study participants are all male and predominantly white, well-educated, and of middle to upper socioeconomic status. There was a lack of information about the type and duration of diabetes.

A total of 2854 men without a history of myocardial infarction or stroke were included in this study and followed for an average of 16 years. The study demonstrated that exercise ECG test results were a strong predictor of CHD mortality risk. The other predictors of CHD death were abnormal resting ECG, obesity (BMI ≥ 30), hypertension, and hypercholesterolemia.

The authors concluded that abnormal exercise ECG response is a significant determinant of CHD mortality in men with diabetes mellitus. Assessment of ECG by maximal stress testing provides important prognostic information independent of cardiorespiratory fitness level and traditional CHD risk factors.

These two studies are consistent in their findings that ECG ST-segment deviation is a significant predictor of cardiac events.

Duke Treadmill Score

One study[44] examined the prognostic value of the Duke Treadmill Score (DTS) in 100 patients with diabetes. None of the patients had a history of coronary heart disease, but 76 had chest pain. Patients who failed to achieve 85% of their predicted maximum heart rate during exercise testing or who had unsatisfactory study results were excluded.

The DTS was calculated as: exercise time – (5 × maximum ST deviation) – (4 × angina index). Thirty-six percent of the patients with diabetes were classified as low-risk (i.e. DTS ≥ 5), 48% were classified as intermediate risk (i.e. DTS between − 10 and 4), and 15% were stratified as high risk (i.e. DTS < − 10). The study demonstrated that survival rates free of major adverse cardiac events (MACE: cardiac death or nonfatal myocardial infarction) differed significantly across risk groups: 97% in the low-risk group, 93% in the intermediate risk group, and 70% in the high-risk group (P = 0.002). The survival rates free of composite events (MACE, revascularization, and congestive heart failure) were 89% in the low-risk group, 54% in the intermediate-risk group, and 13% in the high-risk group (P < 0.0001). The multivariate analysis revealed that the DTS was the only independent predictor of combined event outcomes of cardiac death, nonfatal myocardial infarction, congestive heart failure, or revascularization.

As the authors pointed out, patients with diabetes are a distinct group with respect to exercise testing. These patients are usually obese and have more associated co-morbidities such as hypertension, peripheral neuropathy, peripheral vascular disease, decreased functional capacity, and physical deconditioning, and a higher usage of heart rate–limiting medications such as β-blockers and calcium channel blockers. These factors adversely influence the ability of the patients with diabetes to exercise long enough to achieve a low-risk DTS. The exercise workload that they can achieve, therefore, might not be adequate to induce ischemia and related ECG changes and symptoms despite the presence of significant coronary artery disease, which is more prevalent in patients with diabetes.

Delayed heart rate recovery

One study[46] examined the prognostic value of heart rate recovery (HRR) following a maximum exercise test for cardiovascular disease (CVD) mortality and mortality from all causes in 2333 male patients with diabetes, of whom 218 had a history of CVD at baseline. This article is another one of the multiple publications of the Aerobics Center Longitudinal Study. The study participants are all men and predominantly white, well educated, and of middle to upper socioeconomic status. There was a lack of information about the type and duration of diabetes.

The study found that lower HRR measured 5 minutes following maximal exercise was independently associated with higher CVD death and all-cause mortality in men with diabetes. This association persists even after adjusting for age, cardiorespiratory fitness, prior cardiovascular disease, and other possible confounders. However, cardiorespiratory fitness was a stronger predictor of risk of CVD death compared to HRR. The authors suggested that when assessing risk in men with diabetes, HRR should not be used alone, but rather in conjunction with other strong predictors such as cardiorespiratory fitness.

This ongoing prospective study began in 1970, and thus some important data are lacking. There was no information about the DTS calculation, for example. During the follow-up period, the independent covariates may change and this kind of change will reduce the association between covariates and cardiovascular disease and all-cause death. In addition, there was no information about 1- or 2-minute rates (only 5-minute) of recovery (heart rate at 1 or 2 minutes of recovery is sensitive to detection of the association between HRR and cardiovascular disease events); thus, the study could not determine the relative strengths of prediction of 1-, 2-, or 5-minute HRR values. Furthermore, information on the medications, such as those prescribed for the treatment of hypertension and other cardiovascular diseases that might affect HRR, was incomplete.

Another study[49] also examined the relationship between HRR and cardiovascular events in 871 patients with type 2 diabetes. In contrast to the one just described,[46] this study used 1- and 2-minute HRR as a prognostic variable.

The study demonstrated that individuals with an attenuated HRR (< 12 bpm) at one minute after exercise were older; had longer durations of diabetes, higher rest heart rates, higher systolic blood pressure at entry into the study, and shorter exercise times; and were more likely to have chronotropic incompetency as well as micro-vascular disease (overt albuminuria, retinopathy, or neuropathy at baseline) compared with those patients without attenuated HRR after exercise. After adjusting for traditional risk factors, attenuated 1- and 2-minute HRR remained significantly associated with increased risk of cardiovascular events as compared to those without attenuation. The study concluded that HRR provides information beyond traditional cardiovascular risk factors that could aid in the clinical risk stratification of patients with type 2 diabetes.

The results from these two studies complemented each other as one study provided information on the prognostic value of 1- and 2-minute HRR and the other provided information on the prognostic value of 5-minute HRR. HRR aids in clinical risk stratification of patients with diabetes.

Metabolic equivalents (METs)

Another article from the above-mentioned Aerobics Center Longitudinal Study[45] assessed cardiorespiratory fitness (quantified by maximal METs) as a prognostic variable with a symptom-limited maximal treadmill exercise test in 2316 male patients with diabetes.

This study found an inverse relation between cardiorespiratory fitness and cardiovascular disease mortality within this cohort of men with diabetes, and this association was independent of body mass index. Higher levels of fitness were inversely related to cardiovascular disease mortality in normal weight, overweight, and class 1 obese men with diabetes. Men who were overweight or class 1 obese but were at least moderately fit had lower cardiovascular disease mortality risk compared to men who had normal weight but were physically unfit.

This study also found that other variables such as fasting glucose level, systolic blood pressure, parental history of premature cardiovascular disease, and abnormal exercise ECG (ST-segment depression) were independently predictive of future cardiac events.

The characteristics of the participants, such as being exclusively male and predominantly white, well-educated, and of middle to upper socioeconomic class, limit the ability to generalize the results of this study. As well, the lack of information on the use of medications prevents the evaluation of medications as a possible effect modifier.

Peak VO_2

One study[48] used CPET to measure baseline peak VO_2 in 468 patients with type 2 diabetes who did not have a history of coronary heart disease. These patients underwent graded exercise testing and were followed up for 5 years. All baseline exercise tests and peak VO_2 measurements were performed after 7 to 11 weeks of wash out from any antihypertensive medications. Respiratory exchange ratio (RER), the ratio of carbon dioxide production to oxygen consumption, was used as a measure of exercise intensity. Patients who were unable to reach a RER of 1.0 were excluded from the analysis.

The study found that patients who developed cardiovascular disease events had a significantly lower baseline peak VO_2 (20.3 ± 0.6 mL kg-1 min-1) compared to those who did not (21.9 ± 0.3 mL kg-1 min-1) (P = 0.02). The multiple Cox regression analysis showed that in addition to duration of diabetes and overt albuminuria, low peak VO_2 was also an independent and significant predictor of future clinical cardiovascular disease events (P = 0.0165). Decreased peak VO_2 is therefore one of several pathophysiological mechanisms leading to the time-dependent development of cardiovascular events in patients with type 2 diabetes.

Impaired chronotropic response (CR)

One study[50] examined the association between impaired CR and adverse events among 1341 patients with diabetes referred to exercise treadmill test. Impaired CR is defined as the inability to achieve 85% of predicted maximal heart rate during exercise testing (calculated as 220 minus age).

This study reported that more than one-third of the included patients demonstrated impaired CR during exercise ECG test and found that patients with impaired CR were more likely to have co-morbidities (e.g. hypertension, coronary artery disease, peripheral vascular disease, or CHF) and abnormal HRR during exercise testing. In addition, patients with impaired CR, compared to those with normal CR, were at increased risk of myocardial infarction and revascularization procedures. In the multivariate analysis impaired CR remained significantly associated with increased risk of combined all-cause mortality, myocardial infarction, and revascularization procedures.

This study provided no description of patients' characteristics such as age, gender distribution, BMI, and duration of diabetes, which makes it difficult to generalize the study findings. In addition, the follow-up period was relatively short (less than 5 years).

Safety

None of the five studies described above reported adverse events that occurred during or immediately following exercise testing. No other study was found that specifically addressed the safety issue of exercise stress testing in patients with diabetes.

Guidelines/Consensus Statements/ Position Statement

The 2008 Canadian Diabetes Association Clinical Practice Guidelines[3] has stated that moderate to high levels of physical activity and cardiorespiratory fitness are associated with substantial reductions in morbidity and mortality in both men and women and in both type 1 and type 2 diabetes. Before beginning a program of physical activity more vigorous than walking, however, people with diabetes should be assessed for conditions that might contraindicate certain types of exercise, predispose them to injury, or be associated with an increased likelihood of cardiovascular disease (CVD). Based on expert consensus, the guidelines recommended that an exercise ECG stress test be considered for previously sedentary individuals with diabetes at high risk for CVD who wish to undertake exercise more vigorous than brisk walking.

In 2007, the American Diabetes Association (ADA)[4] recommended that "a graded exercise test with ECG monitoring should be seriously considered before undertaking aerobic physical activity with intensity exceeding the demands of everyday living (more intense than brisk walking) in previously sedentary diabetic individuals whose 10-year risk of a coronary event is likely to be ≥ 10%." These recommendations were also based on expert consensus or clinical experience.

In the fifth edition of "ACSM's resource manual for Guidelines for exercise testing and prescription" published in 2006, the American College of Sports Medicine[53] provided clinical guidelines for patients with diabetes who should undergo a graded exercise test to evaluate his/her cardiac health status before beginning a moderate- to high-intensity exercise program. These patients include: (1) previously sedentary individuals with diabetes aged > 35 years or sedentary at any age, diagnosed with diabetes > 10 years; (2) individuals diagnosed with type 1 diabetes > 15 years or type 2 diabetes > 10 years; (3) individual with additional major risk factors for coronary artery disease such as the presence of smoking, hyperlipidemia, obesity, and being sedentary; (4) individuals with clinically advanced peripheral vascular or renal disease, micro-vascular disease, cardiomegaly, or congestive heart failure; (5) individuals with advanced autonomic, renal, or cerebrovascular disease, and (6) individuals with known advanced coronary artery or carotid occlusive disease. These recommendations were primarily based on an ADA position statement published in 2004[54] that does not reflect current ADA recommendations, and several primary studies; however, it is not clear whether a systematic approach was used to identify clinical research evidence.

According to this resource manual, patients with diabetes may not need an exercise test before starting a very light or light exercise program if they are anticipating exercise activity level approximately equal to his or her walking pace; under age 35 years; without additional major risk factors for coronary artery disease; without additional risk factors for sudden death; and have normal resting ECG. These recommendations were based on the ADA clinical guidelines/ position statement.

The American College of Cardiology/American Heart Association 2002 Guideline Update for Exercise Testing[19] recommended evaluation of asymptomatic persons with diabetes mellitus who plan to start vigorous exercise. This recommendation was based on expert consensus.

Discussion

Summary of results

Five primary studies (with eight published articles) examined the prognostic values of exercise tests for future cardiac events in patients with diabetes. All five studies demonstrated that the prognostic variables under investigation were independent predictors of future cardiac events (fatal or non-fatal). The prognostic variables under investigation varied across the studies. For exercise ECG testing, the prognostic variables included ECG ST-segment deviation, the Duke Treadmill Score, exercise capacity measured by maximal metabolic equivalents, delayed heart rate recovery after exercise testing, and impaired chronotropic response to exercise testing. For CPET, prognostic variables included peak oxygen uptake.

Results from each individual study indicated that ST-segment depression on ECG, low Duke Treadmill Score, delayed heart rate recovery following exercise, low fitness level (measured by METs), reduced peak oxygen uptake during exercise, and impaired chronotropic responses were independent predictors of future cardiac events (fatal and non-fatal). In addition, other variables such as ankle brachial index (one study), fasting glucose, systolic blood pressure, and parental history of premature cardiovascular disease (one study), hypertension, hypercholesterolemia, and abnormal resting ECG (one study), duration of diabetes and overt albuminuria (one study) were also independent and significant predictors of future cardiac events.

These results suggest that the considerable prognostic power of the exercise ECG test lies beyond the ST-segment response and the presence of angina during exercise. Parameters including exercise capacity, heart rate recovery, and impaired chronotropic response to exercise testing offer significant prognostic information, particularly in patients with diabetes who may not experience angina during exercise and who may have increased autonomic dysfunction.[9]

None of the five primary studies reported any adverse events related to exercise testing. None of the included primary studies provided information on whether the cardiac events occurred during exercise.

The literature search did not locate any study that compared the prognostic value of exercise testing with physician's judgment based on medical history and physical examination. Some studies however considered individual variables such as body mass index, blood pressure, and resting heart rate, which are important components of physical examination, in their multivariate analyses.

No study was found that examined the prognostic value of the 6-minute walking test in patients with diabetes. No prognostic study was found for patients with COPD and arthritis.

Methodological issues

A prospective study design is important for prognostic studies. Four of the five primary prognostic studies utilized a prospective cohort study design, whereas only one was a retrospective cohort study, indicating that most of the evidence came from well- designed studies overall.

Ideally, prognostic parameters should be evaluated in a representative sample of patients assembled at a common point in the course of the disease. However, patients were similar in terms of secondary complications of diabetes in only two studies. Furthermore, patient inclusion and exclusion criteria were clearly defined in only two studies, which makes generalizing the research findings difficult.

Although follow-ups were complete or nearly complete in the majority of studies, the length of follow-up appeared to be sufficient (defined as at least 5 years) in only three studies. This might lead to underestimation of the prognostic power of the variables under investigation.

Prognostic studies are prone to publication bias; that is, studies that demonstrate a strong (often statistically significant) prognosis ability are more likely to be published.[41] All of the included primary studies reported statistically significant association between the predictive variables of interest and the clinical endpoints (dependent variables). The true value of the prognostic variables derived from exercise tests might be overestimated because of publication bias.

Given the above-mentioned weakness, the findings from the included studies should be interpreted with caution.

Questions unanswered

The primary question of interest was whether exercise testing could provide additional prognostic information about patients' risk of future cardiac events compared to physicians' judgment based on medical history and physical examination. A cohort study that examined the prognostic value of exercise testing that is incremental to that obtained from medical history and physical examination would help to address this question. However, no study with such a design was found through a comprehensive literature search. Furthermore, even if good clinical judgment may be appropriate in some patients, there is still a need to utilize objective prognostic markers.[55]

None of the studies mentioned whether the clinical endpoints (fatal or non-fatal cardiac events) were observed during or immediately following exercise. The reason for this may be that these studies were not designed to predict the risk of future cardiac events during exercise but to stratify high-risk patients for future interventions; for example, indication for earlier intervention (revascularization) in patients with diabetes.

The information obtained from the included studies may not directly answer the question whether exercise testing could provide additional information about the risk of exercise in patients with chronic diseases. However, these studies still provide some insights that an abnormal exercise test (which could be defined in many different ways: ST-segment depression, low Duke Treadmill Score, reduced metabolic equivalents, delayed heart rate recovery, impaired chronotropic response, reduced peak oxygen uptake, etc.) can provide important prognostic information regarding future cardiac death or non-fatal cardiac events in patients with diabetes. Given that the risk of experiencing cardiac events during vigorous exercise is higher than that at rest and that patients with diabetes have higher prevalence of silent myocardial ischemia on average than most populations, the prognostic variables examined in these studies could be useful for predicting cardiac risk during or immediately after exercise.

The questionnaire Physical Activity Readiness Questionnaire (PAR-Q) was claimed to be a useful tool for evaluating whether a patient is safe to participate in an exercise program. This questionnaire consists of seven questions concerning history and symptoms of heart disease. No study was found that examined the prognostic value of this questionnaire.

Which patient groups can forgo the exercise stress testing?

Recommendations from the Canadian Diabetes Association, the American Diabetes Association, and the American College of Sports Medicine are consistent in that only previously sedentary individuals with diabetes who want to start vigorous (moderate- to high-intensity) exercise need to undergo exercise testing before participating in an exercise program. However, the term *sedentary individual* needs to be defined clearly in the recommendations from these clinical guidelines.

The research findings from the included studies did not provide any guidance on the selection of patients with chronic diseases who can forgo exercise tests prior to vigorous exercise. A clinical expert suggested that an opinion article published in 1996[56] might be helpful in this regard. This article proposed that four groups of patients with chronic diseases may be referred to a cardiopulmonary rehabilitation program without an exercise test. Details of those four groups of patients are provided in Appendix G.

This article also emphasized that patients entering a cardiac rehabilitation program without an entry exercise test should be under close supervision. Their exercise program should be gradually titrated to provide the most efficacious program possible while maintaining the patient within their physical limitations and below their symptomatic threshold. However, no subgroup of patients with diabetes was mentioned in this article.

The best way to predict patients' risk of future cardiac events

There are currently no guidelines on the best way to predict the risk of future cardiac events in patients with chronic diseases such as diabetes, COPD, or arthritis. Physicians' judgment based on medical history and physical examination in combination with exercise testing is recommended but these recommendations are based on expert opinion or consensus.

Although exercise ECG testing or CPET may provide prognostic information for patients with diabetes, only those who are able to exercise or are expected to have interpretable exercise ECGs can undergo exercise testing. A single study involving a non-random sample of middle-aged and older people with long-standing diabetes and at least one other cardiac risk factor demonstrated that the exercise ECG test is either unfeasible or uninterpretable in up to 50% of these patients.[57] However, people with shorter duration of diabetes and fewer risk factors would have a much lower prevalence of inability to exercise or uninterpretable test (Dr. R Sigal, personal communication, January 2009). The exercise ECG test is considered to be uninterpretable when patients have negative clinical and ECG criteria but patients are unable to reach 85% of the maximal predicted heart rate.[57] Other tests, such as pharmacological stress testing, may be useful in some of these patients but the prognostic value of the variables measured by these tests was outside the scope of this report.

Limitations

The present review has several limitations.

The literature review was confined to published reports of systematic reviews and primary studies that were written in English or German and were publicly available. Only full-text articles were included because abstracts provide insufficient details to allow an accurate, unbiased assessment of the study results. The authors of the abstract-only publications were not contacted to request full details because of time constraints.

The methodological quality of the selected cohort studies was assessed using a quality tool, with the expectation that this would aid in identifying the studies that should be given more weight in the overall synthesis. However, the findings from the selected studies were not comparable. The extent of publication bias was not assessed because of the small number of the studies (less than 10) included in this report.

The present review only summarizes the recommendations from relevant clinical practice guidelines and consensus documents and does not appraise their scientific foundations. In some clinical guidelines/position statement documents, the guideline development working groups did not provide information on the methodological approaches used. They were not contacted to determine if the recommendations were based on research evidence.

Qualitative research literature that discussed the benefits and limitations of using exercise testing from physicians' and patients' perspectives was not included in this report because of time constraints.

Conclusion

The evidence presented in this report is from five primary studies that focused on prognostic values of exercise testing in patients with diabetes. No systematic review on this topic or primary studies on patients with COPD and arthritis were found. No study that addressed safety issue of exercise testing was located.

Based on the published evidence, the exercise ECG test and the cardiopulmonary exercise test could provide statistically significant and important prognostic information to predict future cardiac events in patients with diabetes.

No study was found that examined the incremental prognostic value of exercise testing compared to physicians' judgment based on medical history and physical examination in patients with diabetes. For patients with diabetes who often have silent myocardial ischemia, physicians' judgment based on medical history and physical examination may not be sufficient to detect their underlying cardiovascular disease; these patients may be at risk of future cardiac events when participating in a more vigorous exercise program than brisk walking if they are previously physically inactive. Therefore, exercise testing may provide additional prognostic information for risk stratification of those patients with diabetes who are able to undergo exercise testing before entry into a structured community-based exercise program.

Appendix A: Method

Search strategy

A comprehensive literature search was conducted by the IHE Information Specialist between January 2008 and March 2009 to retrieve articles published between 1997 and 2009. The searches were limited to human studies where possible. No language restrictions were applied. Reference lists of relevant articles were also browsed to find more studies. The search strategy was developed and carried out prior to the study selection process.

Medical Subject Headings (MeSH) terms relevant to this topic include: Exercise Test; Chronic Disease, etc.

Table A.1: Search strategy

Database	Edition or date searched	Search Terms ††
Databases		
The Cochrane Library http://www.thecochranelibrary.com	Issue 1, 2009 March 6, 2009	"exercise test" or "exercise tests" or "exercise testing" or "ergometry test" or "ergometry tests" or "stress test" or "stress tests" or "stress testing" or "step test" or "step tests" or "step testing" or "treadmill test" or "treadmill tests" or "treadmill testing" or "stress echocardiography" or "exercise echocardiography" or "walk test" or "walking test" or "walk distance test" or "walking distance test :ti,ab,kw and "chronic disease" or "chronic diseases" or arthritis or diabetes or copd or "chronic obstructive pulmonary disorder" :ti,ab,kw, from 1997 to 2009
MEDLINE	March 6, 2009	1. Exercise Test/ 2. ((exercise or ergometry or step or stress or treadmill) adj2 test$).mp. 3. Echocardiography, Stress/ 4. ((stress or exercise) adj echocardiography).mp. 5. ((walk$ adj2 test$) or 6mwt).mp. 6. or/1-5 7. Chronic Disease/ 8. exp Diabetes Insipidus/ or exp Diabetes Mellitus/ 9. exp Pulmonary Disease, Chronic Obstructive/ or Lung Diseases, Obstructive/ 10. exp Arthritis/ 11. diabetes.mp. 12. (copd or coad or (chronic obstructive adj2 disease)).mp. 13. arthritis.mp. 14. or/7-13 15. 6 and 14 16. limit 15 to (yr="1997 - 2009" and "all adult (19 plus years)")

CRD Databases (DARE, HTA, & NHS EED)	March 6, 2009	1. MeSH Exercise Test 2. "exercise test" OR "exercise tests" OR "exercise testing" OR ergometry OR "step test" OR "step tests" OR "step testing" OR "stress test" OR "stress tests" OR "stress testing" OR "treadmill test" OR "treadmill tests" OR "treadmill testing" OR "walk test" OR "walking test" OR "walk testing" OR "walk distance test" OR "walking distance test" OR 6mwt 3. MeSH Echocardiography, Stress 4. "stress echocardiography" OR "exercise echocardiography" 5. #1 OR #2 OR #3 OR #4 6. MeSH Chronic Disease 7. MeSH Diabetes Mellitus EXPLODE 1 2 8. MeSH Diabetes Insipidus EXPLODE 1 2 9. diabetes 10. MeSH Lung Diseases, Obstructive EXPLODE 1 11. MeSH Arthritis EXPLODE 1 12. arthritis 13. copd OR coad OR "chronic obstructive pulmonary disease" OR "chronic obstructive pulmonary disorder" OR "chronic obstructive lung disease" OR "chronic obstructive lung disorder" OR "chronic obstructive airway disease" OR "chronic obstructive airway disorder" 14. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 15. #5 AND #14 RESTRICT PD 1997 2009
EMBASE –Ovid platform (Licensed resource)	March 6, 2009	1. exercise test/ 2. ((exercise or ergometry or step or stress or treadmill) adj2 test$).mp. 3. stress echocardiography/ 4. exercise electrocardiography/ 5. ((stress or exercise) adj (echocardiography or electrocardiography)).mp. or ((walk$ adj2 test$) or 6mwt).mp. 6. or/1-5 7. Chronic Disease/ 8. exp Diabetes Mellitus/ 9. exp Diabetes Insipidus/ 10. chronic lung disease/ or chronic obstructive lung disease/ 11. exp Arthritis/ 12. diabetes.mp. 13. (copd or coad or (chronic obstructive adj2 disease)).mp. 14. arthritis.mp. 15. or/7-14 16. 6 and 15 17. limit 16 to (yr="1997 - 2009" and (adult <18 to 64 years> or aged <65+ years>))

Web of Science – ISI platform (Licensed resource)	March 9, 2009	"exercise test" OR "exercise tests" OR "exercise testing" OR ergometry OR "step test" OR "step tests" OR "step testing" OR "stress test" OR "stress tests" OR "stress testing" OR "treadmill test" OR "treadmill tests" OR "treadmill testing" OR "stress echocardiography" OR "exercise echocardiography" OR "walk test" OR "walking test" OR "walk testing" OR "walk distance test" OR "walking distance test" OR 6mwt AND "chronic disease" OR "chronic diseases" OR "chronic disorder" OR "chronic disorders" OR diabetes OR arthritis OR copd OR "obstructive pulmonary disease" OR "obstructive pulmonary disorder" OR "obstructive lung disease" OR "obstructive lung disorder" OR "obstructive airway disease" OR "obstructive airway disorder" DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI, A&HCI; Timespan=1997-2009
PEDro	March 9, 2009	"exercise test" AND diabetes; "exercise tests" AND diabetes; "exercise testing" AND diabetes; "stress test" AND diabetes; "stress tests" AND diabetes; "stress testing" AND diabetes; "exercise test" AND arthritis; "exercise tests" AND arthritis; "exercise testing" AND arthritis; "stress test" AND arthritis; "stress tests" AND arthritis; "stress testing" AND arthritis; "exercise test" AND "obstructive pulmonary"; "exercise tests" AND "obstructive pulmonary"; "exercise testing" AND "obstructive pulmonary "exercise test" AND "obstructive lung" "exercise tests" AND "obstructive lung" "exercise testing" AND "obstructive lung" "stress test" AND "obstructive pulmonary"; "stress tests" AND "obstructive pulmonary"; "stress testing" AND "obstructive pulmonary" "stress test" AND "obstructive lung" "stress tests" AND "obstructive lung" "stress testing" AND "obstructive lung" "walk test" AND diabetes "walking test" AND diabetes "walk distance test" "walking distance test"

		6mwt AND diabetes 6mwt AND copd "walk test" AND lung "walking test" AND lung "walk test" AND pulmonary "walking test" AND pulmonary "walk test" AND copd "walking test" AND copd
SPORTDiscus	March 9, 2009	"exercise test" OR "exercise tests" OR "exercise testing" OR ergometry OR "step test" OR "step tests" OR "step testing" OR "stress test" OR "stress tests" OR "stress testing" OR "treadmill test" OR "treadmill tests" OR "treadmill testing" OR "stress echocardiography" OR "exercise echocardiography" OR "walk test" OR "walking test" OR "walk testing" OR "walk distance test" OR "walking distance test" OR 6mwt AND "chronic disease" OR "chronic diseases" OR "chronic disorder" OR "chronic disorders" OR diabetes OR arthritis OR copd OR "obstructive pulmonary disease" OR "obstructive pulmonary disorder" OR "obstructive lung disease" OR "obstructive lung disorder" OR "obstructive airway disease" OR "obstructive airway disorder" 1997-2009
Library Catalogue		
NEOS (Central Alberta Library Consortium)	January 9, 2008	Any field ""exercise test" (also tests and testing)" AND Any field ""chronic disease" or diabetes or arthritis or "obstructive pulmonary disorder" or "obstructive pulmonary disease" or "obstructive lung disorder" or "obstructive lung disease"" Any field ""stress test" (also tests and testing)" AND Any field ""chronic disease" or diabetes or arthritis or "obstructive pulmonary disorder" or "obstructive pulmonary disease" or "obstructive lung disorder" or "obstructive lung disease"" Any field "treadmill" AND Any field ""chronic disease" or diabetes or arthritis or "obstructive pulmonary disorder" or "obstructive pulmonary disease" or "obstructive lung disorder" or "obstructive lung disease"" Any field "echocardiography" AND Any field ""chronic disease" or diabetes or arthritis or "obstructive pulmonary disorder" or "obstructive pulmonary disease" or "obstructive lung disorder" or "obstructive lung disease""

Guidelines		
AMA Clinical Practice Guidelines http://www.topalbertadoctors.org/guidelines/guidelinespdf.aspx	December 19, 2007	List of CPGs was reviewed. No guidelines found.
CMA Infobase http://mdm.ca/cpgsnew/cpgs/index.asp	December 19, 2007	Exercise test; stress test; step test; ergometry; treadmill; echocardiography
National Guideline Clearinghouse http://www.ngc.gov	December 19, 2007	Exercise test AND diabetes; "exercise test" AND "chronic disease"; "stress test" AND diabetes; "stress test" AND "chronic disease"; "exercise testing"; "stress testing" Results saved in search folder under 'Grey lit search results'
Clinical Trials		
ClinicalTrials.gov (US) http://clinicaltrials.gov/	January 11, 2008	Exercise test AND chronic disease AND cardiac; Exercise test AND diabetes AND cardiac; Exercise test AND arthritis AND cardiac; Exercise test AND COPD AND cardiac; Exercise test AND obstructive pulmonary disease AND cardiac; Stress test AND chronic disease AND cardiac Stress test AND diabetes AND cardiac; Stress test AND arthritis AND cardiac; Stress test AND COPD AND cardiac; Stress test AND obstructive pulmonary disease AND cardiac; Echocardiography AND chronic disease AND cardiac Echocardiography AND diabetes AND cardiac; Echocardiography AND arthritis AND cardiac; Echocardiography AND COPD AND cardiac; Echocardiography AND obstructive pulmonary disease AND cardiac Ergometry; ergometer Results saved in search folder.
CenterWatch Clinical Trials Listing Service http://www.centerwatch.com/	January 11, 2008	Exercise test (s;ing); stress test (s;ing); echocardiography; treadmill; step test; ergometry; ergometer No relevant results found.
metaRegister of Controlled Trials (mRCT) http://www.controlled-trials.com/mrct/	January 11, 2008	Exercise test (s;ing); stress test (s;ing); echocardiography; treadmill; step test; ergometry, ergometer Results saved in search folder.

National Research Register https://portal.nihr.ac.uk/Pages/NRRArchive.aspx	January 14, 2008	Exercise test (s;ing); stress test (s;ing); stress echocardiography; exercise echocardiography; treadmill; step test; ergometry; ergometer Relevant results saved in search folder.
UK Clinical Research Network Portfolio Database http://pfsearch.ukcrn.org.uk/	January 14, 2008	Exercise test (s;ing); stress test (s;ing); echocardiography; treadmill; step test (s;ing) No relevant results found.
HTA resources		
AETMIS http://www.aetmis.gouv.qc.ca	January 2, 2008	Exercise test (s;ing); stress test (s;ing); ergometry; step test (s;ing); treadmill test (s;ing); echocardiography; walk(ing) test(s;ing); 6MWT No results found.
CADTH http://www.cadth.ca	January 2, 2008	Exercise; stress; echocardiography; ergometry; ergometer; treadmill; walk test; 6MWT No relevant results found.
Institute for Clinical and Evaluative Sciences (ICES), Ontario http://www.ices.on.ca/	January 2, 2008	Exercise test (s;ing); stress test (s;ing); stress echocardiography; exercise echocardiography; treadmill; ergometer; ergometry; step test (s;ing); walk test; 6MWT Results saved in Search folder.
Health Technology Assessment Unit At McGill http://www.mcgill.ca/tau/	January 2, 2008	Browsed list of reports. No relevant results found.
Medical Advisory Secretariat http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html	January 2, 2008	Browsed list of recommendations. No relevant results found.
CCE http://www.med.monash.edu.au/healthservices/cce/	January 2, 2008	Browsed list of reports. No relevant results found.
ECRI http://www.ecri.org (Licenced Resource)	January 2, 2008	exercise test (s;ing); stress test (s;ing); ergometry; step test (s;ing); treadmill test (s;ing) No relevant results found.
Health Quality Council, Saskatchewan http://www.hqc.sk.ca/	January 2, 2008	Exercise test (s;ing); stress test (s;ing); ergometry; step test (s;ing); treadmill test (s;ing); electrocardiography; 6MWT; walk test(s;ing) No relevant results found.
NZHTA http://nzhta.chmeds.ac.nz/publications.htm	January 14, 2008	Browsed list of publications. No relevant results found.
NICE (UK) http://www.nice.org.uk/	January 14, 2008	Exercise; stress; echocardiography; ergometry; ergometer; treadmill; 6mwt; walk test(s;ing)

Association Websites Searched	
February 2008	• American Diabetes Association • Canadian Diabetes Association • International Diabetes Federation • American Association of Cardiovascular and Pulmonary Rehabilitation • American College of Cardiology • American Heart Association • Canadian Association of Cardiac Rehabilitation • Canadian Cardiovascular Society • European Society of Cardiology • International Society for Heart Research • Society of Geriatric Cardiology • Canadian Society for Exercise Physiology • Canadian Arthritis Network • American College of Sports Medicine • American Medical Society for Sports Medicine • Canadian Academy of Sports Medicine • International Federation of Sports Medicine • Canadian Council of Sports Medicine • Canadian Lung Association • Arthritis Society of Canada

Note: †† "*", "# ", and "?" are truncation characters that retrieve all possible suffix variations of the root word; e.g. surg* retrieves surgery, surgical, surgeon, etc.

; are used to separate search terms that were searched separately.

Study selection

One information specialist (PC) scanned all titles and abstracts identified from the literature search and excluded the ones that appeared to be irrelevant. One researcher (BG) reviewed the remaining abstracts and retrieved full-text articles for further examination. The retrieval was limited to published studies written in English or German. Copies of the full-text articles were reviewed by one researcher (BG) and key research studies were selected according to the following pre-determined inclusion and exclusion criteria.

Inclusion criteria

Study design: systematic reviews of prospective cohort studies, primary studies including prospective or retrospective cohort studies.

An article was deemed to be a systematic review if it met all of the following criteria as defined by Cook et al.:[43]

- focused clinical question;
- explicit search strategy;

- use of explicit, reproducible, and uniformly applied criteria for article selection;
- critical appraisal of the included studies; and
- qualitative or quantitative data synthesis.

Population: adult patients (18 years or older) with any of the following chronic diseases/conditions: diabetes (type 1 or type 2), COPD, or arthritis (rheumatoid arthritis or osteoporosis).

Intervention: exercise test including exercise ECG test, cardiopulmonary stress test, or 6-minute walking test.

Comparator: physician's judgment based on medical history and physical examination.

Outcome: at least one of the following:

- Safety outcome: any cardiac events occurred during or immediately after exercise testing;
- Prognostic value of exercise testing in predicting any of the following cardiac events: major adverse cardiac events (cardiac death, acute myocardial infarction), other milder cardiac events (e.g. new-onset angina).

Full-text articles in the English or German languages published from 1997 onward (The literature search was limited the publications in the past 10 years because of time constraints.)

Exclusion criteria

Study design: conference abstracts, letters, news, commentaries.

Population: patients younger than 18 years old.

Intervention: other types of exercise tests (e.g. pharmacological or isotopic stress test), dobutamine stress echocardiography, combination of cardiac stress testing with other exercise testing but results not reported separately.

Outcome: correlation of prognostic variables with other tests or only all-cause mortality reported.

In some cases, closer examination of the full-text of the article revealed that it did not meet the inclusion criteria specified by the review protocol. Consequently, these papers, listed in Table C.1, were not included to formulate the evidence base for the systematic review. However, where appropriate, relevant information contained in the excluded papers was used to inform other sections of the report and to expand the review discussion.

Data extraction

One researcher (BG) abstracted data from each of the included studies according to a standardized data extraction form developed a *priori*. A second assessor (CH) fact-checked the evidence table to ensure accuracy and consistency of the data extracted.

Methodological quality assessment

The selected research studies were critically appraised with respect to various methodological aspects using a 10-item quality assessment checklist along with a dictionary developed by the research team. This checklist addresses six important aspects of prognostic studies: study design, study participants, follow-up, prognostic factor measurement, outcome measures, and analysis. Because of the limitations of using numerical scores to rate the quality of prognostic studies, each criterion was rated as yes, no, partial or unclear (Appendix D).

Two researchers (BG, MO) independently assessed the methodological quality of the five selected studies (eight articles) to minimize the risk of judgment errors. The two reviewers discussed the checklist and the dictionary with respect to the interpretation of the questions prior to assessing the studies. Any disagreement between the two researchers was resolved according to a predefined strategy using consensus and arbitration as appropriate. A statistical measure of the inter-rater agreement for quality assessment was not performed.

Critical appraisal results for all selected studies are presented in Appendix D. The evidence was not graded but was described in terms of potential sources of bias that should be taken into account when interpreting the reported results.

Data analysis and synthesis

Information from each of the included studies was summarized qualitatively in this review. It was not possible to perform a meta-analysis because of the small number of studies, different prognostic variables under investigation, and different outcome measures.

External review

External reviewers with clinical expertise in exercise testing and/or health technology assessment methodologies evaluated the draft report and provided feedback. In selecting reviewers, the practice of the Institute of Health Economics is to choose experts who are well recognized and have published widely in peer-reviewed literature, and who can offer a provincial and/or national perspective with respect to the use of exercise tests.

Appendix B: Living Well Exercise Test Triage

(Source: Aspen Health Region, 2007)

Abbreviations for Figure 1

ACSM – American College of Sports Medicine

BMI – body mass index

CABG – coronary artery bypass graft

CAD – coronary artery disease

C-era – private stress testing clinic

CKD – chronic kidney disease

CPET – cardiopulmonary exercise testing

CVA – cerebral vascular accident (stroke)

CVD – coronary vascular disease

CWIC – Cardiac Wellness Institute of Calgary

F – female

GXT – graded exercise test (stress test in this context)

IFG – impaired fasting glucose

LW – Living Well program

M – male

MD – medical doctor

METs – metabolic equivalents

MI – myocardial infarction

mo – month

PAD – peripheral artery disease

PCTA – percutaneous transluminal angiography/angioplasty

PVD – peripheral vascular disease

RGH – Rockyview General Hospital

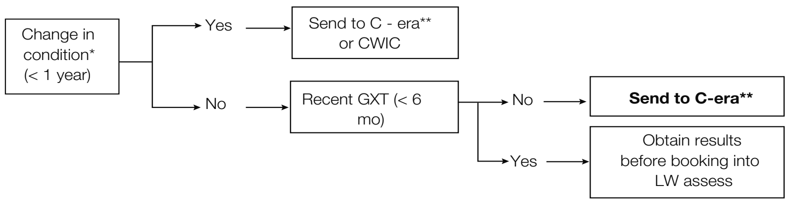
TIA – transient ischemic attack

TM – treadmill

WG – waist girth

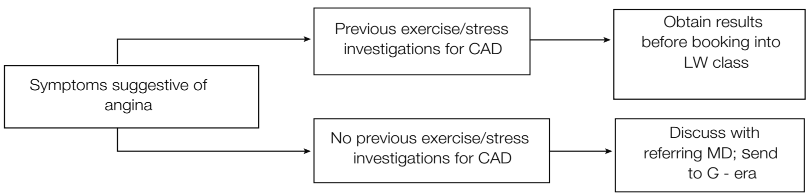
Figure 1: Living well exercise test triage

1. Known coronary artery disease, PAD, or CVA/TIA (if no, go to #2)

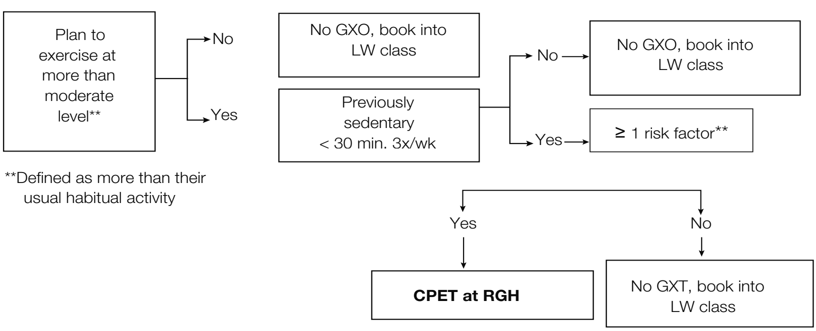


**For patients with CVA/CVD/PVD, if physical function if very limited (< 3 METs) and TM or bike test is not feasible, and patient is asymptomatic, no exercise test is necessary.

2. Symptoms suggestive of angina – no known CAD (if no, go to #3)

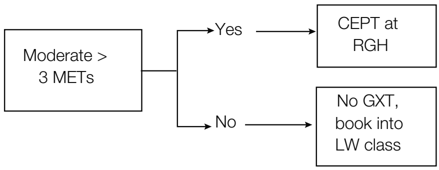


3. Known diabetic (if no, go to #4)

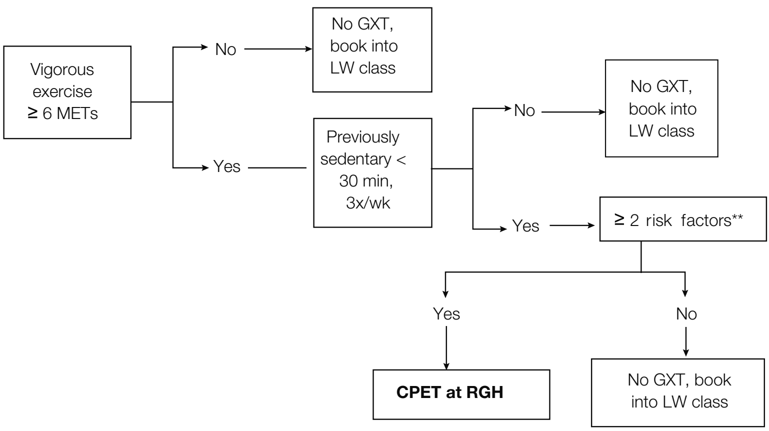


Note: if capacity at RGH to handle volumes and ECG interpretation/safety screening in place then 50% will be sent to RGH.

4. Known COPD, CKD, or CHF



5. Hypertension, dyslipidemia, and obesity



Definitions
*Change in Condition (within the past year)
New event – MI
**Defined as more than their
New Intervention – CABG, PCTA, valve repair, replacement, other cardiac surgery usual habitual activity
Change or increase in symptoms – angina or other symptoms suggestive of CVD

Risk factors (ACSM)
Family history
Cigarette smoking
Hypertension
Dyslipidemia
IFG
Obesity (BMI > 30, or WG >102 cm M and > 88 cm F)
Sedentary lifestyle

Exercise levels
3 METs = walking (2.5 mph)
6 METs = brisk walking (3.5 mph & uphill)

GXT – graded exercise test

Appendix C: Excluded Studies

Table C.1: Excluded studies and reasons for exclusion

Excluded study	Reason for exclusion
Al-Attar AT et al. Cardiac tests in asymptomatic type 2 diabetics. *Medical Principles & Practice* 2002;11(4):171-75	Did not focus on the prognostic value of exercise testing
Bacci et al. Screening for silent myocardial ischaemia in type 2 diabetic patients with additional atherogenic risk factors: applicability and accuracy of the exercise stress test. *European Journal of Endocrinology* 2002;147(5):649-54	Did not focus on the prognostic value of exercise testing
Bacci et al. Heart rate response during positive exercise stress test predicts coronary artery disease and its severity in high- risk type 2 diabetic patients with silent ischemia. *Diabetes Care* 2003;26(9):2698-99	Letter
Charvat et al. [Relation between diabetes compensation, albuminuria and biochemical parameters and the results of stress myocardial SPECT in asymptomatic type 2 diabetics]. *Vnitrni Lekarstvi* 2004;50(12):894-900	Focused on diagnostic but not prognostic value of exercise testing
Choi et al. Prognostic significance of asymptomatic coronary artery disease in patients with diabetes and need for early revascularization therapy. *Diabetic Medicine* 2007;24(9):1003-11	Included diabetic patients with coronary artery disease; did not focus on prognostic value of exercise testing.
Church et al. Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care* 2004;27(1):83-8	Clinical outcome was all-cause mortality
Cosson et al. Detecting silent coronary stenoses and stratifying cardiac risk in patients with diabetes: ECG stress test or exercise myocardial scintigraphy? *Diabetic Medicine.* 2004;21(4):342-48	Focused on exercise myocardial scintigraphy
Ellis et al. Is systolic blood pressure recovery after exercise a predictor of mortality? *American Heart Journal* 2004;147(2):287-92	Study participants were not patients with chronic diseases of interest
Enright et al. The 6-min walk test: a quick measure of functional status in elderly adults. *Chest* 2003;123(2):38798	Study participants were not with defined chronic diseases
Faglia et al. Cardiac events in 735 type 2 diabetic patients who underwent screening for unknown asymptomatic coronary heart disease: 5-year follow-up report from the Milan Study on Atherosclerosis and Diabetes (MiSAD). *Diabetes Care* 2002;25(11):2032-36	Focused on exercise myocardial scintigraphy
Faglia et al. Risk reduction of cardiac events by screening of unknown asymptomatic coronary artery disease in subjects with type 2 diabetes mellitus at high cardiovascular risk: an open-label randomized pilot study. *American Heart Journal* 2005;149(2):E1-E6	Focused on diagnosis and treatment, not on prognostic value of exercise testing
Fornengo et al. Prevalence of silent myocardial ischaemia in new-onset middle-aged Type 2 diabetic patients without other cardiovascular risk factors. *Diabetic Medicine* 2006;23(7):775-9	Did not focus on the prognostic value of exercise testing
Georgoulias et al. Evaluation of abnormal heart-rate recovery after exercise testing in patients with diabetes mellitus: correlation with myocardial SPECT and chronotropic parameters. *Nuclear Medicine Communications* 2007;28(3):165-71	Did not focus on the prognostic value of exercise testing

Excluded study	Reason for exclusion
Gokcel et al. Silent coronary artery disease in patients with type 2 diabetes mellitus. *Acta Diabetologica* 2003;40(4):176-80	Focused on the prevalence of silent coronary artery disease
Hayashi et al. The treadmill exercise-tolerance test is useful for the prediction and prevention of ischemic coronary events in elderly diabetics. *Journal of Diabetes & Its Complications* 2005;19(5):264-8	Less than half of the participants had diabetes; did not focus on the prognostic value of exercise testing
Hayashino et al. Cost-effectiveness of coronary artery disease screening in asymptomatic patients with type 2 diabetes and other atherogenic risk factors in Japan: factors influencing on international application of evidence-based guidelines (Provisional record). *International Journal of Cardiology* 2007;118(1):88-96	Did not focus on the prognostic value of exercise testing
Hayashino et al. Cost-effectiveness of screening for coronary artery disease in asymptomatic patients with Type 2 diabetes and additional atherogenic risk factors. *Journal of General Internal Medicine* 2004;19(12):1181-91	Did not focus on the prognostic value of exercise testing
Hiraga et al. Prognostic predictors for survival in patients with COPD using cardiopulmonary exercise testing. Clinical Physiology and Functional Imaging 2003;23 (6): 324-31	Clinical outcome was all-cause mortality
Inoguchi et al. High incidence of silent myocardial ischemia in elderly patients with non insulin-dependent diabetes mellitus. *Diabetes Research & Clinical Practice* 2000;47(1):37-44	Did not focus on the prognostic value of exercise testing
Janand-Delenne et al. Silent myocardial ischemia in patients with diabetes: who to screen. *Diabetes Care* 1999;22(9):1396-1400	Did not focus on the prognostic value of exercise testing
Kallinen et al. The predictive value of exercise testing for survival among 75-year-old men and women. *Scandinavian Journal of Medicine & Science in Sports* 2006;16(4):237-44	Study participants were not patients with chronic diseases of interest
Lacasse et al. Post-exercise heart rate recovery and mortality in chronic obstructive pulmonary disease. Respiratory Medicine 2005;99:877-86	Clinical outcome was all-cause mortality
Laukkanen et al. The predictive value of cardiorespiratory fitness combined with coronary risk evaluation and the risk of cardiovascular and all-cause death. *Journal of Internal Medicine* 2007;262(2):263-72	Study participants were not patients with chronic diseases of interest
Laukkanen et al. Systolic blood pressure during recovery from exercise and the risk of acute myocardial infarction in middle-aged men. *Hypertension* 2004;44(6):820-5	Study participants were not patients with chronic diseases of interest
Laukkanen et al. The predictive value of cardiorespiratory fitness combined with coronary risk evaluation and the risk of cardiovascular and all-cause death. *Journal of Internal Medicine* 2007;262(2):263-72	Study participants were not patients with chronic diseases of interest
Lee et al. Clinical utility of the exercise ECG in patients with diabetes and chest pain. *Chest* 2001;119(5):1576-81	Did not focus on the prognostic value of exercise testing

Excluded study	Reason for exclusion
May et al. Cardiovascular autonomic neuropathy in insulin-dependent diabetes mellitus: prevalence and estimated risk of coronary heart disease in the general population. *Journal of Internal Medicine* 2000;248(6):483-91	Did not focus on the prognostic value of exercise testing
May et al. Prevalence and prediction of silent ischaemia in diabetes mellitus: a population-based study. *Cardiovascular Research* 1997;34(1):241-7	Did not focus on the prognostic value of exercise testing
McAuley et al. Exercise capacity and body mass as predictors of mortality among male veterans with type 2 diabetes. *Diabetes Care* 2007;30(6):1539-43	Clinical outcome was all-cause mortality (causes of death not specified)
Myers et al. Fitness versus physical activity patterns in predicting mortality in men. *American Journal of Medicine* 2004;117(12):912-18	Study participants were not patients with chronic diseases of interest
Ong and Ong Cardiopulmonary exercise testing in patients with chronic obstructive pulmonary disease. *Annals of the Academy of Medicine, Singapore* 2000;29(5):648-52	Did not focus on the prognostic value of exercise testing
Penfornis et al. Use of dobutamine stress echocardiography in detecting silent myocardial ischaemia in asymptomatic diabetic patients: a comparison with thallium scintigraphy and exercise testing. Diabetic Medicine 2001;18(11):900-5	Did not focus on the prognostic value of exercise testing
Rutter et al. Silent myocardial ischemia and microalbuminuria in asymptomatic subjects with non-insulin-dependent diabetes mellitus. *American Journal of Cardiology* 1999;83(1):27-31	Did not focus on the prognostic value of exercise testing
Sejil et al. Six-year follow-up of a cohort of 203 patients with diabetes after screening for silent myocardial ischaemia. *Diabetic Medicine* 2006;23(11):1186-91	Used exercise or imaging testing but the results not reported separately
Seshadri et al. Association of diabetes mellitus with abnormal heart rate recovery in patients without known coronary artery disease. *American Journal of Cardiology* 2003;91(1):108-11	Did not focus on the prognostic value of exercise testing
Seshadri et al. Association of an abnormal exercise heart rate recovery with pulmonary function abnormalities. *Chest* 2004;125(4):1286-91	Did not focus on the prognostic value of exercise testing
Sukhija et al. Silent myocardial ischaemia in patients with type II diabetes mellitus and its relation with autonomic dysfunction. *Indian Heart Journal* 2000;52(5):540-6	Did not focus on the prognostic value of exercise testing
Takigawa et al. Distance and oxygen desaturation in 6-min walk test predict prognosis in COPD patients. *Respiratory Medicine* 2007;101:561-7	Clinical outcome was all-cause mortality
Tojo et al. Pulmonary exercise testing predicts prognosis in patients with chronic obstructive pulmonary disease. *Internal Medicine* 2005;44(1):20-5	Clinical outcomes were not cardiac events
Ugur-Altum et al. Factors related to exercise capacity in asymptomatic middle-aged type 2 diabetic patients. *Diabetes Research & Clinical Practice* 2005;67(2):130-6	Did not focus on the prognostic value of exercise testing
Vacanti et al. In comparison to the myocardial perfusion scintigraphy, a treadmill stress test is a viable, efficient and cost effective option to predict cardiovascular events in elderly patients. *Arquivos Brasileiros de Cardiologia* 2007;88(5):531-6	Study participants were not patients with chronic diseases of interest
Valensi et al. Predictive value of silent myocardial ischemia for cardiac events in diabetic patients: influence of age in a French multicenter study. *Diabetes Care* 2005;28(11):2722-27	Used exercise or imaging testing but the results not reported separately

Excluded study	Reason for exclusion
Valensi et al. Predictive value of cardiac autonomic neuropathy in diabetic patients with or without silent myocardial ischemia. *Diabetes Care* 2001;24(2):339-43	Used exercise or imaging testing but the results not reported separately
Valensi et al. Silent myocardial ischaemia and left ventricle hypertrophy in diabetic patients. *Diabetes & Metabolism* 1997;23(5):409-16	Did not focus on the prognostic value of exercise testing
Vanzetto et al. Prediction of cardiovascular events in clinically selected high-risk NIDDM patients. Prognostic value of exercise stress test and thallium-201 single-photon emission computed tomography. *Diabetes Care* 1999;22(1):19-26	Used exercise or imaging testing but the results not reported separately
Wackers et al. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care* 2004;27(8):1954-61	Focused on the prevalence, not prognostic value of exercise testing
Wei et al. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. *Annals of Internal Medicine* 2000;132(8):605-11	Clinical outcome was all-cause mortality (causes of death not specified)
Williams et al. Exercise duration and peak systolic blood pressure are predictive of mortality in ambulatory patients with mild-moderate chronic heart failure. *Cardiology* 2005;104(4):221-6	Clinical outcome was all-cause mortality (causes of death not specified)

Appendix D: Quality Assessment Results

Quality assessment checklist (Adapted from Altman, 2001[41] Hyden et al. 2006,[51] Doust et al. 2005[52])

Study design

1. Were data collected prospectively?

Study participation

2. Were inclusion/exclusion criteria defined?

3. Were the patients recruited at a common point in their disease?

To be answered yes, ≥ 80% patients either with or without known cardiovascular disease and other secondary complications for diabetes.

Follow-up

4. Was follow-up sufficiently long for the clinical outcome?

To be answered yes, the patients should have been followed up 5 years or longer.

5. Was follow-up complete?

To be answered yes, follow-up should have been completed in 80% or more of the participants.

Prognostic factor measurement

6. Was the method for measuring prognostic factors defined?

Outcome

7. Were outcomes of interest clearly defined?

To be answered yes, a clear definition of outcomes of interest should be provided.

8. Were outcomes measured "blind"?

To be answered yes, outcomes should be measured without knowing the patients' clinical characteristic and prognostic factors.

Analysis

9. Were continuous predictor variables analyzed appropriately?

To be answered yes, a cut-off point for continuous data should not be determined by a data dependent process (i.e. exploring all cut-off points to find the one that minimizes the P value).

10. Was statistical adjustment performed for most important prognostic factors?

To be answered yes, statistical adjustment should have been performed for most important prognostic factors, that is, age, gender, plus at least one of other clinically relevant factors such as smoking, blood pressure, heart rate, or body mass index.

Table D.1: Methodological quality assessment results

Study feature	Quality criteria	Rutter et al.[14]	Lakkireddy et al.[44]	Cheng et al.[46]	Church et al.[45]
Study design	Data collected prospectively	+	+	+	+
Study participation	Inclusion/exclusion criteria defined	?	+	?	+
	Recruited at a common point in their disease	-	+	+	+
Follow-up	Sufficiently long for the clinical outcome	-	+	+	+
	Follow-up complete	+	+	+	+
Prognostic variable measurement	Method for measuring prognostic factors defined	+	+	+	+
Outcome	Outcomes of interest clearly defined	+	?	+	+
	Outcomes measured blind	+	+	+	+
Analysis	Continuous predictor variable analyzed appropriately	+	+	+	+
	Statistical adjustment for all important prognostic factors	+	+	+	+
Total number of "yes" responses		7	9	9	10

+: yes; -: no; ?: partial or unclear

Table D1: Methodological quality assessment results (cont'd)

Study feature	Quality criteria	Lyerly et al.[47]	Seyoum et al.[48]	Chacko et al.[49]	Ho et al.[50]
Study design	Data collected prospectively	?	+	-	+
Study participation	Inclusion/exclusion criteria defined	+	?	?	-
	Recruited at a common point in their disease	+	-	-	?
Follow-up	Sufficiently long for the clinical outcome	+	+	+	-
	Follow-up complete	+	+	+	+
Prognostic variable measurement	Method for measuring prognostic factors defined	+	+	+	+
Outcome	Outcomes of interest clearly defined	+	?	+	?
	Outcomes measured blind	?	+	+	?
Analysis	Continuous predictor variable analyzed appropriately	+	+	+	?
	Statistical adjustment for all important prognostic factors	+	+	+	+
Total number of "yes" responses		8	7	7	4

Appendix E: Summary of Results From the Selected Prognostic Studies

Table E.1: Prognostic studies for diabetes

Study	Patient	Intervention	Results
Rutter et al. 2002[14] United Kingdom **Study design**: prospective cohort **Objective**: to investigate the relationship between future coronary heart disease events and baseline SMI and microalbuminuria in patients with type 2 diabetes free from known CHD	**Total No.**: 86 **Age** (yrs): 62 ± 7 (range 46 to 74) **Gender** (M/F): 62/24 **Disease**: type 2 diabetes **Duration of DM** (yrs): median 7 (1 to 23) BMI (kg/M2): 29.8 ± 5.0 **History of CVD**: none **Smoking status**: current (20.9%), past (52.3%), never (26.7%) **Secondary complications**: microalbuminuria (50%), neuropathy (26.7%), retinopathy (31.4%) **Co-morbidity**: NA **Treatment**: medical treatment: β-blockers at baseline (10.5%)	**Exercise testing** *Types*: exercise (treadmill) ECG test *Prognostic variable*: ST-segment depression *Criteria for abnormal test*: ECG change (> 1 mm downsloping or horizontal ST-segment depression from baseline occurring 0.08 seconds after the J point for 3 consecutive beats) *Follow-up*: median 2.8 yrs (range 1.3 to 4.9), none lost to follow-up (100% follow-up rate)	**Frequency of cardiac events**: Total: 23 events in 15 patients (17%) Cardiac death: 3 AMI: 7 events New-onset angina: 13 events **Relationship of prognostic variables to cardiac events**: *Univariate analysis*: Ankle brachial index (ABI) (as a continuous variable) (P = 0.014) SMI (P = 0.02) Microalbuninuria (P = 0.046) Framingham 10-year CHD risk > 30% (P = 0.035) Fibrinogen (g/l) (as a continuous variable) (P = 0.026) *Multivariate analysis*: HR (95% CI): SMI: 21 (2–204) (P = 0.008) ABI: 17 (1.3–213) (P = 0.032)

Continuous data are expressed as mean ± standard deviation unless otherwise indicated.

Abbreviations: ABI: Ankle brachial index; AMI: acute myocardial infarction; bpm: beats per minute; CHD: coronary heart disease; CI: confidence interval; CPET: cardiopulmonary exercise test; CVD: cardiovascular disease; DM: diabetes; DTS: Duke Treadmill Score; ECG: electrocardiogram; F: female; HR: hazard ration; HRR: heart rate recovery; M: male; MACE: major adverse cardiac events; METs: metabolic equivalents; MI: myocardial infarction; NA: not available; No.: number; SMI: silent myocardial ischemia; VO2: oxygen uptake.

Table E.1: Prognostic studies for diabetes (cont'd)

Study	Patient	Intervention	Results
Lyerly et al. 2008[47] United States **Study design:** Analysis of previously prospectively collected data **Objective:** to examine the association between exercise ECG responses and CHD and CVD mortality in patients with diabetes	**Total No.**: 2854 **Age** (yrs): 49.5 ± 9.7 (range 21 to 84) **Gender** (M/F): 2854/0 **Disease:** diabetes **Duration of DM** (yrs)**:** NA **BMI** (kg/M2): mean 28 **History of CVD:** no history of MI or stroke **Smoking status:** current (18.6%) **Secondary complications:** NA **Co-morbidity:** hypertension (43.5) **Treatment:** NA	**Exercise testing** **Types:** maximal symptom-limited treadmill exercise test with a modified Balke protocol **Prognostic variable:** ST-segment depression **Criteria for abnormal test:** ECG change (≥ 1 mm ST-segment depression or elevation that lasted ≥ 0.08 seconds from the J point) **Follow-up:** mean 15.8 (SD 9.6, range 1.3 to 30.0) yrs	**Frequency of cardiac events:** Total death: 441 210 deaths due to CVD, 133 deaths due to CHD **Relationship of prognostic variables to cardiac events:** **Multivariate analysis:** HR (95% CI): Equivocal exercise ECG test: 2.11 (1.29 to 3.46) Abnormal exercise ECG test: 3.00 (1.95 to 4.61) BMI ≥ 30: 2.81 (1.76 to 4.51) Hypertension: 2.15 (1.50 to 3.18) Hypercholesterolemia: 1.46 (1.04 to 2.07)

Table E.1: Prognostic studies for diabetes (cont'd)

Study	Patient	Intervention	Results
Lakkireddy et al. 2005[44] United States **Study design:** prospective cohort **Objective:** to determine whether the Duke Treadmill Score (DTS) has the same predictive capacity in patients with diabetes as it does in the general population	**Total No.**: 100 **Age** (yrs): 59 ± 10 **Gender** (M/F): 58/42 **Disease**: diabetes **Duration of DM** (yrs): NA **BMI** (kg/M2): 31 ± 6 **History of CVD**: none **Smoking status**: current (16%) **Secondary complications**: NA **Co-morbidity**: hypertension (67%), hypercholesterolemia (37%) **Treatment**: anti-anginal medication: β blockers (17%), calcium channel blockers (43%)	**Exercise testing**: *Types*: Exercise (treadmill) ECG test using standard Bruce protocol *Prognostic variable*: DTS *Criteria for abnormal test*: DTS ≥ 5 (low risk), –10 to 4 (intermediate risk), < –10 (high risk) **Follow-up**: median 6.6 yrs (none lost to follow-up)	**Frequency of cardiac events**: MACE (death or MI): 8 patients (8%) Revascularization or CHF: 39 patients (39%) **Relationship of prognostic variables to cardiac events**: Survival free of MACE (death or MI) differed significantly across risk groups (P = 0.002); survival free of composite event (MACE, CHF, or revascularization) differed significantly across risk groups (P < 0.001) Multivariate analysis: DTS was the only independent predictor of combined event outcomes in patients with diabetes (P < 0.001)

Table E.1: Prognostic studies for diabetes (cont'd)

Study	Patient	Intervention	Results
Cheng et al. 2003[46] United States **Study design**: prospective cohort **Objective**: to evaluate whether slow HRR after maximal exercise predicts cardiovascular disease and all-cause mortality among diabetic men	**Total No.**: 2333 **Age** (yrs): 49.4 ± 9.5 (range 23 to 79) **Gender** (M/F): 2333/0 **Disease**: diabetes **Duration of DM** (yrs): NA **BMI** (kg/M2): mean 27.5 **History of CVD**: 218 (9.3%) **Smoking status**: current (20.5%), past (44.4%), never (35.1%) **Secondary complications**: NA **Co-morbidity**: hypertension (51.6%), hypercholesterolemia (41.9%), CAD (9.3%) **Treatment**: NA	**Exercise testing**: *Types*: Symptom-limited maximal treadmill exercise testing using a modified Balke protocol, continuous ECG monitoring *Prognostic variable*: HRR (defined as the heart rate decline during the first 5 min following completion of the maximal exercise test) *Criteria for abnormal test*: quartile 1 (< 55 bpm), quartile 2 (55 to 66 bpm), quartile 3 (67 to 75 bpm), quartile 4 (> 75 bpm) **Follow-up**: median 14.9 (range 1 to 25) yrs (none lost to follow-up)	**Frequency of cardiac events**: CVD mortality: 142 (6.1%) **Relationship of prognostic variables to cardiac events**: Lower HRR associated with higher cardiac mortality *Univariate analysis (adjusted for age)*: Cardiorespiratory fitness (METs): (likelihood ratio $\chi2$ = 35.3) HRR: (likelihood ratio $\chi2$ = 31.3) *Multivariate analysis*: HR (95% CI) (adjusted for other variables): For HRR as categorical variable (in quartile) HRR < 55 bpm: HR = 2.0 (1.1 to 3.8) HRR 55 to 66 bpm: HR = 1.5 (0.8 to 2.7) HRR 67 to 75 bpm: HR = 1.5 (0.9 to 2.8) P value for trend = 0.007 For HRR as a continuous variable (10-bpm decrease): HR=1.2 (1.1 to 1.4)

Table E.1: Prognostic studies for diabetes (cont'd)

Study	Patient	Intervention	Results
Chacko et al. 2008[49] United States **Study design**: retrospective cohort **Objective**: to evaluate the relationship of 1- and 2-min HRR and the incidence of all-cause and CV mortality and CV events in patients with type 2 diabetes	**Total No.**: 871 **Age** (yrs): 58.5 ± 8.2 **Gender** (M/F): 549/322 **Disease**: type 2 diabetes **Duration of DM** (yrs): 8.8 ± 7.0 BMI (kg/M2): 31.4 ± 5.5 **History of CVD**: 218 (9.3%) **Smoking status**: current smoker (13.8%) **Secondary complications**: macrovascular disease (29.6%), microvascular disease (68.5%) **Co-morbidity**: NA **Treatment**: NA	**Exercise testing**: *Types*: modified Bruce protocol, monitoring of symptoms, HR, BP, and ECG changes *Prognostic variable*: HRR: defined as the value between the HR at peak exercise and minus the value at 1 or 2 min into the recovery period (1-min HRR, 2-min HRR) Chronotropic incompetence: defines as the inability to reach 85% of predicted maximal HR (calculated as 220 – age in years) *Criteria for abnormal test*: HRR < 12 bpm 1-min HRR (bpm): quintal 1 (≤ 12), quintal 2 (13 to 18), quintal 3 (19 to 22), quintal 4 (23 to 28), quintal 5 (> 28) 2-min HRR (bpm): quintal 1 (<28), quintal 2 (29 to 36), quintal 3 (37 to 42), quintal 4 (43 to 49), quintal 5 (> 49) **Follow-up**: 5 yrs (none lost to follow-up)	**Frequency of cardiac events**: Cardiovascular mortality: 35 Cardiovascular events (non-fatal MI, cerebrovascular accident, CHF requiring hospital admission): 135 patients (15.5%) **Relationship of prognostic variables to cardiac events**: Lower HRR associated with higher cardiovascular mortality and cardiovascular events HR (95% CI) for HRR as categorical variable (in quintile) **1-min HRR** *For cardiovascular mortality*: HRR ≤12 bpm: HR = 1.0 (reference) HRR 13 to 18 bpm: HR = 0.8 (0.3 to 2.1) HRR 19 to 22 bpm: HR = 0.4 (0.1 to 1.4) HRR 23 to 28 bpm: HR = 0.4 (0.1 to 1.4) HRR > 28 bpm: HR = 1.6 (0.6 to 4.0) *For cardiovascular events* HRR ≤12 bpm: HR = 1.0 (reference) HRR 13 to 18 bpm: HR = 0.5 (0.3 to 0.8) (P < 0.01) HRR 19 to 22 bpm: HR = 0.6 (0.4 to 1.0) (P < 0.05) HRR 23 to 28 bpm: HR = 0.5 (0.4 to 0.9) (P < 0.05) HRR > 28 bpm: HR = 1.0 (0.6 to 1.5) **2-min HRR** *For cardiovascular mortality*: HRR ≤ 28 bpm: HR = 1.0 (reference) HRR 29 to 36 bpm: HR = 0. (0.3 to 1.5) HRR 37 to 42 bpm: HR = 0.2 (0.04 to 0.9)(P < 0.05) HRR 43 to 49 bpm: HR = 0.4 (0.1 to 1.3) HRR > 49 bpm: HR = 1.0 (0.3 to 2.8) *For cardiovascular events* HRR ≤28 bpm: HR = 1.0 (reference) HRR 29 to 36 bpm: HR = 0.8 (0.5 to 1.1) HRR 37 to 42 bpm: HR = 0.5 (0.3 to 0.8) (P < 0.01) HRR 43 to 49 bpm: HR = 0.6 (0.4 to 1.0) HRR > 49 bpm: HR = 1.2 (0.8 to 1.9)

Church et al. 2005[45] United States **Study design**: prospective cohort **Objective**: to examine (1) the risk of CVD mortality associated with fitness level and BMI, (2) the dose-response relationship between categories of fitness and CVD mortality within levels of BMI, and (3) the shape of the fitness-CVD mortality curve when fitness is quantified by increments of maximal metabolic equivalents (METs)	**Total No.**: 2316 **Age** (yrs): 50 ± 10 **Gender** (M/F): 2316/0 **Disease**: type 1 and type 2 diabetes **Duration of DM** (yrs): NA **BMI** (kg/M2): 26.8 ± 3.4 **History of CVD**: NA **Smoking**: current (20.5%), past (44.3%), never (35.2%) **Secondary complications**: NA **Co-morbidity**: hypertension (31.9%) **Treatment**: NA	**Exercise testing**: *Types*: Symptom-limited maximal treadmill exercise test using a modified version of the protocol of Balke and Ware, continuous ECG monitoring *Prognostic variable*: maximal METs *Criteria for abnormal test*: fitness level defined as low (lowest 20%), moderate (middle 40%), or high (upper 40% of the previously defined age-specific distribution of maximal exercise duration) **Follow-up**: 15.9 ± 7.9 yrs (range 1 to 27.7 yrs)	**Frequency of cardiac events**: CVD mortality: 179 (7.7%) **Relationship of prognostic variables to cardiac events**: *Multivariate analysis*: HR (95% CI): Maximal MET obtained (per 1-MET increment): 1.2 (1.10 to 1.32) (P < 0.001) Fasting glucose level (per 10-mg/dL increment): 1.04 (1.02 to 1.06) (P < 0.001) Systolic blood pressure (per 10-mm Hg increment): 1.10 (1.01 to 1.19) Parental history of premature CVD: 1.72 (1.20 to 2.50) (P = 0.004) Abnormal exercise ECG (ST-depression): 2.2 (1.55 to 3.09) (P < 0.001)

Table E.1: Prognostic studies for diabetes (cont'd)

Study	Patient	Intervention	Results
Seyoum et al. 2006[48] United States **Study design**: prospective cohort **Objective**: to determine the predictive value of baseline peak exercise oxygen consumption on subsequent development of cardiovascular events in patients with type 2 diabetes	**Total No.**: 468 **Age** (yrs): mean 57.6 **Gender** (M/F): 307/161 **Disease**: type 2 diabetes **Duration of DM** (yrs): mean 9.1 **BMI** (kg/M2): mean 31.2 **History of CVD**: none **Smoking** (pack yrs): mean 19.7 **Secondary complications**: retinopathy (52.1%), nephropathy (15.2%) **Co-morbidity**: hypertension (100%) **Treatment**: NA	**Exercise testing**: *Type*: exercise treadmill test using a Half Bruce protocol *Prognostic variable*: peak VO2 *Criteria for abnormal test*: NA **Follow-up**: 5 yrs (none lost to follow-up)	**Frequency of cardiac events**: Cardiac death, non-fatal MI, non-fatal cerebral vascular accident, HF requiring hospitalization, and pulmonary infarction: 71 patients (15.2%) **Relationship of prognostic variables to cardiac events**: *Baseline peak* VO2 (mL kg-1 min-1): 20.3 ± 0.6 in patients who developed cardiac events vs. 21.9 ± 0.3 in patients who did not (P = 0.02) *Multivariate analysis*: HR (95% CI): Peak VO2: 0.931 (0.879 to 0.987) (P = 0.0165) Duration of diabetes: 1.047 (1.016 to 1.079) (P = 0.0027) Overt albuminuria: 2.174 (1.244 to 3.798) (P = 0.0064)

Table E.1: Prognostic studies for diabetes (cont'd)

Study	Patient	Intervention	Results
Ho et al. 2008[50] United States **Study design**: prospective cohort **Objective**: to assess the association between impaired chronotropic response (CR) and adverse events among patients with diabetes referred for exercise treadmill testing	**Total No.**: 1341 **Age** (yrs): NA **Gender** (M/F): NA **Disease**: diabetes **Duration of DM** (yrs): NA **BMI** (kg/M2): NA **History of CVD**: NA **Smoking status**: NA **Secondary complications**: NA **Co-morbidity**: NA **Treatment**: NA	**Exercise testing**: *Types*: symptom-limited exercise treadmill test, the Bruce protocol used in 85% of tests, monitoring of symptoms, HR, BP, and ECG changes and METs *Prognostic variable*: Impaired CR: defined as achievement of < 80% of a patient's heart rate reserve, calculated as (220 – age) – resting heart rate, at peak exercise, or < 62% for patients taking β-blockers within 72 hours of exercise testing **Follow-up**: up to 4.6 yrs (99% of patients completed follow-up)	**Frequency of cardiac events**: MI: 31 patients (2.3%) (3.3% in impaired CR vs. 1.7% in normal CR (P = 0.06) Revascularization procedure: 23.8% in impaired CR vs. 11.7% in normal CR (P < 0.01) **Relationship of prognostic variables to cardiac events**: HR (95% CI) For all-cause mortality, MI, or revascularization procedure: For all patients: HR = 1.53 (1.10 to 2.14) For patients with low risk DTS: HR = 1.36 (0.85 to 2.20) For patients with intermediate risk DTS: HR = 1.95 (1.15 to 3.31)

Appendix F: Covariates Considered in the Included Prognostic Studies

Table F.1: Covariates considered in the univariate analysis

Study	Covariate
Rutter et al.[14] Exercise ECG test	Age, gender, BMI, duration of DM, smoking status, baseline claudication, BP, total cholesterol, high-density lipoprotein cholesterol, HbA1c, fibrinogen, AER, microalbuminuria, positive exercise test, ABI, echocardiographically determined left ventricular mass index, No. of abnormal autonomic function tests, HR variability, and calculated Framingham coronary risk
Lakkireddy et al.[44] Exercise ECG test	Age, gender, BMI, smoking, peak HR, peak systolic BP, peak diastolic BP, peak rate pressure product, hypertension, hyperlipidemia, use of χ-blockers, calcium channel blockers, nitrates
Cheng et al.[46] Exercise ECG test	Age, BMI, smoking status, systolic and diastolic BP, resting HR, cardiorespiratory fitness (METs), fasting glucose, cholesterol, and triglyceride levels, alcohol intake, prior history of CVD
Church et al.[45] Exercise ECG test	BMI, parental history of premature CVD, systolic BP, fasting glucose level, total cholesterol level, cigarette smoking, abnormal resting and exercise ECGs
Lyerly et al.[47] Exercise ECG test	Age, BMI, smoking status, systolic and diastolic BP, resting HR, fasting glucose level, hypercholesterolemia, hypertension, abnormal resting ECG responses, family history of CVD or diabetes, HR reserve, and treadmill time
Seyoum et al.[48] CPET	Age, gender, duration of DM, duration of hypertension, BP, overt albuminuria, total serum cholesterol
Chacko et al.[49] Exercise ECG test	Age, gender, duration of diabetes, duration of exercise, chronotropic incompetency, baseline systolic BP, urinary albumin excretion, total cholesterol, smoking status, study drug (either enalapril or nisoldipine), and BP goal (intensive or moderate)
Ho et al.[50] Exercise ECG test	Demographic factors: age, gender, Clinical factors: smoking status, history of CHD, cerebral vascular disease, peripheral vascular disease, obstructive sleep apnea, diabetes, hypertension, lipid disorders, depression, and congestive heart failure, Treadmill variables: DTS, abnormal HRR, and ventricular ectopy in recovery

Abbreviations: ABI: ankle brachial index; AER: albumin excretion rate; BMI: body mass index; BP: blood pressure; CAD: coronary artery disease; CPET: cardiopulmonary exercise test; CVD: cardiovascular disease; DM: diabetes mellitus; DTS: Duke Treadmill Score; ECG: electrocardiogram; HbA1c: glycosylated hemoglobin; HR: heart rate; METs: metabolic equivalents.

Appendix G: Patients With Chronic Diseases Who May Forego Exercise Testing

McConnell[56] proposed that four groups of patients with chronic diseases may be referred to a cardiopulmonary rehabilitation program without an exercise test:

- Patients with extreme muscle weakness and deconditioning may be unable to exert adequate exercise effort during an exercise test. This might include the elderly, those who have been inactive for prolonged periods, or those with prolonged bed rest.
- Patients with orthopedic limitations may not be able to give an adequate exercise effort to ensure a valid test result. This includes patients with arthritis, amputees, or patients with past stroke/functional defects.
- An exercise test for patients who have left ventricular systolic dysfunction who are limited by shortness of breath as demonstrated during their in-hospital or home exercise program may only indicate what is already known.
- An entry exercise test may not offer any new information for patients with known coronary artery disease and stable angina whose exercise limitations and disease status are well documented.

References

1. Tremblay MS, Shephard RJ, Brawley LR. Research that informs Canada's physical activity guides: an introduction. *Applied Physiology, Nutrition, & Metabolism = Physiologie Appliquee, Nutrition et Metabolisme* 2007;32:S1-S8.
2. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C. Physical activity/exercise and type 2 diabetes. *Diabetes Care* 2004;27(10):2518-39.
3. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Canadian Journal of Diabetes* 2008;32(Suppl 1):S1-S201.
4. American Diabetes Association. Standards of medical care in diabetes - 2007. *Diabetes Care* 2007;30(Suppl 1):S4-S41.
5. International Diabetes Federation. Diabetes: a global threat. Available at: *http://www.eatlas.idf.org/webdata/docs/background_opening_pc.pdf* 2008 [accessed 2008 Nov 6].
6. Health Canada. Type 2 diabetes. Available at: *http://www.hc-sc.gc.ca/hl-vs/alt_formats/pacrb-dgapcr/pdf/iyh-vsv/diseases-maladies/diabete-eng.pdf* 2008 [accessed 2008 Nov 10].
7. Johnson JA, Vermeulen SU, Hugel G. *Alberta diabetes Atlas* 2007. Edmonton, AB: Institute of Health Economics; 2007.
8. International Diabetes Federation. *Diabetes Atlas. Executive Summary.* Brussels, Belgium: International Diabetes Federation; 2003. Report No.: Second Edition.
9. Albers AR, Krichavsky MZ, Balady GJ. Stress testing in patients with diabetes mellitus. Diagnostic and prognostic value. *Circulation* 2006;113:583-92.
10. Harris GD, White RD. Exercise stress testing in patients with type 2 diabetes: when are asymptomatic patients screened? *Clinical Diabetes* 2007;25(4):126-30.
11. Cosson E, Attali JR, Valensi P. Markers for silent myocardial ischemia in diabetes. Are they helpful? *Diabetes & Metabolism* 2005;31(2):205-13.
12. Tardif JC. Cardiac investigation in patients with diabetes. *Canadian Journal of Cardiology* 2006;22:38A-40A.
13. Poirier P, Despres JP, Bertrand OF. Identifying which patients with diabetes should be tested for the presence of coronary artery disease - The importance of baseline electrocardiogram and exercise testing. *Canadian Journal of Cardiology* 2006;22:9A-15A.

14. Rutter MK, Wahid ST, McComb JM, Marshall SM. Significance of silent ischemia and microalbuminuria in predicting coronary events in asymptomatic patients with type 2 diabetes. *Journal of the American College of Cardiology* 2002;40(1):56-61.

15. Nieman DC. *Exercise testing and prescription. A health-related approach.* 6th ed. Boston MA: McGraw-Hill; 2007.

16. Plotnikoff RC, Taylor LM, Wilson PM, Courneya KS, Sigal RJ, Birkett N, et al. Factors associated with physical activity in Canadian adults with diabetes. *Medicine & Science in Sports & Exercise* 2006;38(8):1526-34.

17. Zhao GF, Ford ES FAU, Li CF, Mokdad AH. Compliance with physical activity recommendations in US adults with diabetes. *Diabetic Medicine* 2008;25(2):221-7.

18. Norton K. Applying the sports medicine Australia pre-exerclse screening procedures: Who will be excluded? *Journal of Science and Medicine in Sport* 1998;1(1):38-51.

19. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Available at: *www.acc.org/clinical/guidelines/exercise/dirIndex.htm* 2002.

20. Franklin BA, Gordon S, Timmis GC, O'Neill WW. Is direct physician supervision of exercise stress testing routinely necessary? *Chest* 1997;111:262-5.

21. Giri SF, Thompson, Thompson PD, Kiernan FJ, Clive JF, Fram DB, Mitchel JF, et al. Clinical and angiographic characteristics of exertion-related acute myocardial infarction. *JAMA* 1999;282(18):1731-6.

22. Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, et al. Exercise standards for testing and training. A statement for healthcare professionals from the American Heart Association. *Circulation* 2001;104:1694-740.

23. European Society of Cardiology. Heart failure matters - Glossary. Available at: *http://www.heartfailurematters.org/English_Lang/single/Pages/Glossary* 2007.

24. Brubaker PH, Myers J. *Cardiorespiratory assessment of high-risk or diseased populations.* In: Roitman JL, editor. ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription. 4th ed. Baltimore,ML: Lippincott Williams & Wilkins; 2001. p. 367-75.

25. Mooss A, Gordon NF. *Conceptual basis for coronary artery disease risk factor assessment in clinical practice.* In: Roitman JL, editor. ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription. 4th ed. Baltimore, ML: Lippincott Williams & Wilkins; 2001. p. 3-16.

26. Froelicher VF, Stahr SG. *General principles of exercise testing*. In: Skinner JS, editor. Exercise Testing and Exercise Prescription for Special Cases. Theoretical Basis and Clinical Application. 3rd ed. Baltimore MD: Lippincott Williams & Wilkins; 2005. p. 3-21.

27. Kallinen M, Kauppinen M, Era P, Heikkinen E. The predictive value of exercise testing for survival among 75-year-old men and women. *Scandinavian Journal of Medicine & Science in Sports* 2006;16(4):237-44.

28. Institute for Clinical Systems Improvement. *Cardiac stress test supplement.* Bloomington, MN: Institute for Clinical Systems Improvement (ICSI); 2007. Report No.: 7th Edition.

29. Mottram CD. Exercise testing. *Respiratory Care Clinics of North America* 1997;3(2):247-72.

30. Singh VN. The role of gas analysis with exercise testing. *Primary Care - Clinics in Office Practice* 2001;28(1):159-79.

31. Ingle L. Theoretical rationale and practical recommendations for cardiopulmonary exercise testing in patients with chronic heart failure. *Heart Failure Reviews* 2007;12(1):12-22.

32. ATS/ACCP statement on cardiopulmonary exercise testing. *American Journal of Respiratory and Critical Care Medicine* 2003;167(2):211-77.

33. Weisman IM, Zeballos RJ. Clinical exercise testing. *Clinics in Chest Medicine* 2001;22(4):679.

34. Francis DP, Shamim W, Davies LC, Piepoli MF, Ponikowski P, Anker SD, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO(2) slope and peak VO(2). *European Heart Journal* 2000;21(2):154-61.

35. Johnson JE. Which exercise test should be used for patients with symptomatic COPD? *Chest* 2004;126(3):668-70.

36. Jenkins SC. 6-Minute walk test in patients with COPD: clinical applications in pulmonary rehabilitation. *Physiotherapy* 2007;93(3):175-82.

37. Myers J, Voodi L, Umann T, Froelicher VF. A survey of exercise testing: methods, utilization, interpretation, and safety in the VAHCS. J*ournal of Cardiopulmonary Rehabilitation* 2000;20(4):251-8.

38. Fletcher RH, Fletcher SW, Wagner EH. *Clinical epidemiology. The essentials.* 3 ed. Media, PA: Williams & Wilkins; 1996.

39. Evidence Based Medicine Toolkit. Available at: *http://www.ebm.med.ualberta.ca/ 2008* (accessed 2008 Oct 21).

40. Norman RG, Streiner DL. *PDQ. PrettyDarnedQuick statistics.* 3rd ed. Hamilton ON: BC Decker Inc.; 2003.

41. Altman DG. Systematic reviews of evaluations of prognostic variables. *BMJ* 2001;323(7306):224-8.

42. Mould RF. *Multivariate analysis: The Cox proportional hazards model.* In: Mould RF, editor. Introductory medical stastistics.Bristol; Philadelphia: Institute of Physics Publishing Ltd; 1998. p. 213-31.

43. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of Internal Medicine* 1997;126(5):376-80.

44. Lakkireddy DR, Bhakkad J, Korlakunta HL, Ryschon K, Shen X, Mooss AN, et al. Prognostic value of the Duke Treadmill Score in diabetic patients. *American Heart Journal* 2005;150(3):516-21.

45. Church TS, Lamonte MJ, Barlow CE, Blair SN. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. *Archives of Internal Medicine* 2005;165(18):2114-20.

46. Cheng YJ, Lauer MS, Earnest CP, Church TS, Kampert JB, Gibbons LW, et al. Heart rate recovery following maximal exercise testing as a predictor of cardiovascular disease and all-cause mortality in men with diabetes. *Diabetes Care* 2003;26(7):2052-7.

47. Lyerly GW, Sui X, Church TS, Lavie CJ, Hand GA, Blair SN. Maximal exercise electrocardiography responses and coronary heart disease mortality among men with diabetes mellitus. *Circulation* 2008;117(21):2734-42.

48. Seyoum B, Estacio RO, Berhanu P, Schrier RW. Exercise capacity is a predictor of cardiovascular events in patients with type 2 diabetes mellitus. *Diabetes & Vascular Disease Research* 2006;3(3):197-201.

49. Chacko KM, Bauer TA, Dale RA, Dixon JA, Schrier RW, Estacio RO. Heart rate recovery predicts mortality and cardiovascular events in patients with type 2 diabetes. *Medicine & Science in Sports & Exercise* 2008;40(2):288-95.

50. Ho PM, Maddox TM, Ross C, Rumsfeld JS, Magid DJ. Impaired chronotropic response to exercise stress testing in patients with diabetes predicts future cardiovascular events. *Diabetes Care* 2008;31(8):1531-3.

51. Hayden JA, Cote P, Cote PF, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Annals of Internal Medicine* 2006;144(6):427-37.

52. Doust JA, Pietrzak E, Dobson AF, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. *BMJ* 2005;330(7492):625.

53. Lampman RM, Campaigne BN. *Exercise testing in patients with diabetes.* In: American College of Sports Medicine, editor. ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription. 5 ed. Baltimore, MD: Lippincott Williams & Wilkins; 2006. p. 245-54.

54. American Diabetes Association. Physical activity/exercise and diabetes. *Diabetes Care* 2004;27(Suppl 1):S58-S62.

55. Isnard R, Pousset F, Trochu J, Chafirovskaia O, Carayon A, Golmard J, et al. Prognostic value of neurohormonal activation and cardiopulmonary exercise testing in patients with chronic heart failure. *American Journal of Cardiology* 2000;86(4):417-21.

56. McConnell TR. Exercise prescription: when the guidelines do not work. *Journal of Cardiopulmonary Rehabilitation* 1996;16(1):34-7.

57. Cosson E, Paycha F, Paries J, Cattan S, Ramadan A, Meddah D, et al. Detecting silent coronary stenoses and stratifying cardiac risk in patients with diabetes: ECG stress test or exercise myocardial scintigraphy? *Diabetic Medicine* 2004;21(4):342-8

IHE Publications

For additional copies of IHE Publications, please contact info@ihe.ca or visit www.ihe.ca.

IHE Consensus Statements

Consensus Statement on Depression in Adults: How to Improve Prevention, Diagnosis and Treatment (2008)
Consensus Statement on Healthy Mothers, Healthy Babies: How to Prevent Low Birth Weight (2007)
Consensus Statement on Self-monitoring in Diabetes (2006)

IHE Briefs

2009

Comparative Effectiveness: An Overview

IHE Book Series

Chronic Pain: A Health Policy Perspective (2008)
Cost Containment and Efficiency in National Health Systems: A Global Comparison (2008)
Financing Health Care: New Ideas for a Changing Society (2007)

IHE Reports

2009

Exercise Testing for the Prediction of Cardiac Events in Patients with Diabetes
Effectiveness of Organizational Interventions for the Prevention of Occupational Stress
Assistive Reproductive Technologies: A Literature Review and Database Analysis

2008

Air Ambulance with Advanced Life Support
Effective Dissemination of Findings from Research - A Compilation of Essays
Health Technology on the Net (Tenth Edition)
IHE In Your Pocket: A Handbook of Health Economic Statistics
Spousal Violence Against Women: Preventing Recurrence
The Importance of Measuring Health-related Quality of Life
Using Fetal Fibronectin to Diagnose Pre-term Labour
How Much Should We Spend on Mental Health?
CT and MRI Services in Alberta: Comparisons with Other Health Care Systems
Islet Transplantation For The Treatment Of Type 1 Diabetes – An Update
Determinants and Prevention of Low Birth Weight: a Synopsis of the Evidence
Comparative Effectiveness: An Overview

2007

World In Your Pocket: A Handbook of International Health Economic Statistics
Mental Health Economic Statistics In Your Pocket (Revised)
Cost-effectiveness in the Detection of Syphilis
Economics of Childhood Immunization in Canada: Databook
Evidence of Benefits from Telemental Health: A Systematic Review
Health Technology on the Net (Ninth Edition)
Routine Pre-operative Tests – Are They Necessary?
Screening Newborns for Cystic Fibrosis
Screening Newborns for Hearing
The Use and Benefits of Teleoncology
The Use of Nitric Oxide in Acute Respiratory Distress Syndrome
The Use of Videoconferencing for Mental Health Services in Canada and Finland

2006

Health Technology on the Net (Eighth Edition)
IHE In Your Pocket: A Handbook of Health Economic Statistics

This report on Exercise Testing for the Prediction of Cardiac Events in Patients with Diabetes examines the clinical research evidence on the prognostic value of exercise testing (including electrocardiogram exercise testing and cardiopulmonary exercise testing) for the prediction of cardiac events in patients with diabetes.

INSTITUTE OF HEALTH ECONOMICS
ALBERTA CANADA

Institute of Health Economics
1200 – 10405 Jasper Avenue
Edmonton, AB Canada T5J 3N4

Tel. 780.448.4881 Fax. 780.448.0018
info@ihe.ca

www.ihe.ca

ISBN: 978-1-897443-56-9 (print)
ISBN: 978-1-897443-57-6 (on-line)