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Editorial

Pre-exercise Stress Testing in Type 2 Diabetes: Another Case of Choosing Wisely?

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See article by Armstrong et al., pages 185–192 of this issue.

Patients with type 2 diabetes have an increased risk of cardiovascular disease,[1] thereby leading to heightened concerns that exercise might trigger ischemia[2] and adverse cardiovascular events.[3] In fact, the American College of Sports Medicine updated recommendations[4] for exercise preparticipation health screening suggest that physically inactive patients with either symptoms suggestive of and/or known cardiovascular, metabolic, or renal disease obtain medical clearance before engaging in exercise, independent of the intensity. Despite this, a clear knowledge gap remains when evaluating the "clinical utility" of pre-exercise stress testing. A growing number of studies on the long-term clinical effect of screening for coronary artery disease have used computed tomography angiography,[5] radionuclide myocardial perfusion imaging,[6] and electrocardiography,[7] and reported no association with a reduction in cardiovascular events. As an example, the randomized controlled trial by **D**etection of Silent Myocardial **I**schemia in **A**symptomatic **D**iabetic Subjects (DIAD) study investigators, in which asymptomatic patients (n = 1123) with type 2 diabetes were randomly assigned to screening for coronary artery disease using adenosine-stress radionuclide myocardial perfusion imaging, showed that low cardiac event rates were not reduced with screening over a 4.8-year follow-up period.[6] Although there is an understandable rationale behind the implementation of screening for coronary artery disease in patients with type 2 diabetes, the question remains whether the data support this approach. On the basis of the current literature gap, one could argue that pre-exercise risk stratification of patients with type 2 diabetes has led to an excessive burden of unnecessary medical testing within the health care system, as well as an unnecessary hurdle for patients who plan to initiate an exercise program. Therefore, the following question needs to be addressed: Does pre-exercise stress testing (eg, using a Bruce protocol treadmill test) reduce adverse cardiovascular outcomes among all patients with type 2 diabetes, or as clinicians, should we rethink our risk stratification and referral approach?

Evaluating the Clinical Utility of Pre-exercise Stress Testing: Does a "One Size, Fits All" Approach Work?

In this issue of the *Canadian Journal of Cardiology*, Armstong and colleagues[8] conducted a retrospective cohort study to evaluate whether pre-exercise stress testing is associated with reductions in adverse cardiovascular events in community-dwelling patients with type 2 diabetes who were referred to an 8-week, medically supervised exercise program (2007-2012). A secondary objective was to determine the predictors of cardiovascular events and if referral for stress testing led to a change in care by comparing the characteristics of patients referred for stress testing who had reported a cardiovascular event with those who did not. Chart review was performed to obtain clinical characteristics and comorbidities data, type(s) of tests performed, and outcomes of the testing. On the basis of a pre-exercise stress test algorithm, patients were referred for pre-exercise stress testing (Bruce protocol treadmill test) only if they were sedentary and had > 1 other cardiac risk factor (including symptoms indicative of angina), thereby enabling a reference group of patients with type 2 diabetes who did not undergo stress testing before exercise program initiation. Data on adverse cardiovascular outcomes were collected from provincial databases and defined as cardiac catheterization, revascularization, cardiovascular-related hospital admissions, and cardiovascular-related death. The study authors reported remarkably low rates of major cardiovascular outcomes in patients with type 2 diabetes (< 1% for both groups), with no differences in tested and untested patients during a mean follow-up period of 3.4 years (1.4 years); thereby suggesting that pre-exercise stress testing for the detection of coronary artery disease did not reduce the number of cardiovascular events. Patients identified with a cardiovascular outcome tended to be older men with a clinical history of myocardial infarction, stroke, arrhythmias,

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and/or congestive heart failure. Moreover, a false negative result was also reported in 6 patients who had adverse cardiovascular events despite completing a stress test and medical clearance to exercise. Study findings led to the conclusion that pre-exercise stress testing is not necessary for most asymptomatic patients with type 2 diabetes.

Strengths and Weaknesses of the "Clinical Utility of Pre-exercise Stress Testing in Patients With Type 2 Diabetes" Study

The current study by Armstrong and colleagues[8] has several notable clinical implications, alongside a few limitations, which require discussion. Previous studies have shown that the benefits of exercise rehabilitation for patients with type 2 diabetes extend beyond "hard" clinical events, and include clinically significant improvements in cardiorespiratory fitness (ie, the peak capacity for oxygen uptake and utilization to meet the metabolic demands), quality of life, and risk factor control.[9,10] Therefore, it is important to contextualize the intended purpose of the referral for pre-exercise stress testing. As reported in this study, pre-exercise stress testing might have limited "clinical utility" for detecting hard cardiovascular end points within a short-term, follow-up period. However, this does not address the benefits derived by objectively measured cardiorespiratory fitness data, which is considered "best practice" to inform cardiac disease prevention and rehabilitation. Yang and Oh[9] observed that a 6-month exercise rehabilitation focused program, which has a standardized protocol for pre-exercise stress testing for patients with type 2 diabetes, showed significant improvements in cardiorespiratory fitness (15%), fasting blood glucose (13%), and body mass index (2%). Similarly, the **Look A**ction for **Hea**lth in **D**iabetes (Look AHEAD)[11] also reported superior improvements in body mass (8.6%) and glycemic control (5% improvement in A1c values from 7.3% to 6.9%) after a randomized, controlled trial of patients with type 2 diabetes enrolled in a physical activity and lifestyle-intensive intervention relative to a nonexercise-based diabetes support and education intervention.

A second limitation of the study by Armstrong and colleagues[8] is the exclusion of asymptomatic patients with a low cardiorespiratory fitness (incapable of achieving > 3 metabolic equivalents) from the clinical exercise program and stress testing in the current study. The exclusion of patients with low cardiorespiratory fitness might inadvertently underestimate the clinical utility of pre-exercise stress testing in screening for coronary artery disease (because on the basis of Bayesian theory, intermediate pretest probability or higher patients are the ones most appropriately screened using a stress test). In particular, these patients with low cardiorespiratory fitness might exhibit a higher risk of coronary artery disease and derive greater benefits (eg, greater relative improvement in cardiorespiratory fitness to perform activities of daily living, and greater risk factor control) when a clinical exercise prescription has been on the basis of preclinical stress testing.[12]

One final controversial issue raised by Armstrong and colleagues concerns the recommendation that pre-exercise stress testing might be indicated for patients with type 2 diabetes who wish to engage in vigorous and competitive exercise. At present, there are insufficient data concerning higher-intensity exercise and cardiovascular events among patients with type 2 diabetes to support this indication. A retrospective analysis of nearly 4900 coronary artery disease patients enrolled in a supervised cardiac rehabilitation program reported an event rate of 1 nonfatal myocardial infarction per 23,182 hours of high-intensity interval training.[13] It is speculative that the cardiovascular event risk during acute exercise is less than or equal to that in this report, because current pharmacological treatments for type 2 diabetes[14] are purposely targeted toward the prevention of cardiac-related disease progression.

Conclusions

Regular exercise represents a first-line therapy in the treatment of most patients with type 2 diabetes.[10] However, a growing number of studies have reported that pre-exercise screening does not reduce adverse cardiovascular events among asymptomatic adults with type 2 diabetes. The current study by Armstrong and colleagues[8] provides a novel contribution to this body of literature, with data to challenge the current practice of a broad, standardized pre-exercise stress testing program; thereby suggesting that patients with type 2 diabetes should be referred for pre-exercise stress testing only if they have symptoms suggestive of ischemia, a previous diagnosis of coronary artery disease, arrhythmias, chronic heart failure, microvascular complications, and/or in patients for whom vigorous exercise is planned. The advantage of revising the current risk stratification would be to reduce important factors relevant to any screening program (such as cost, unnecessary follow-up testing after a false positive result). This change in clinical practice must be weighed against the fact that pre-exercise stress testing remains a "gold standard" approach to determine cardiorespiratory fitness and inform a clinical exercise prescription to maximize the dose-response of regular exercise in patients with type 2 diabetes. On the basis of the current study, pre-exercise stress testing might be particularly important for screening and clinical exercise prescriptions among patients with comorbid conditions and/or possibly adults with low cardiorespiratory fitness, which warrants further evaluation.

As clinicians, now is the time to rethink the "clinical utility" of pre-exercise stress testing. The current study findings provide an important message to inform clinical practice, particularly "choosing wisely" when referring asymptomatic patients for clinical exercise stress testing. However, multiple questions remain unanswered—for example: Should all patients with type 2 diabetes be indicated for pre-exercise stress testing? (On the basis of this study, probably not). Is pre-exercise clinical stress testing valuable for informing clinical exercise prescription? (Not tested with this study, but a resounding yes). In conclusion then, the current study suggests that as a broad screening program, there is limited utility for pre-exercise stress testing in a large number of asymptomatic patients with type 2 diabetes and good exercise capacity. However, in selected individuals, and in those for whom the data will be used to provide a formal exercise prescription, a pre-exercise stress testing program might provide benefits outside "hard" cardiovascular end points, such as improved cardiorespiratory fitness, improved quality of life, and better risk factor control. As always, when considering referral for any test, it is imperative to recognize the potential

questions being answered, and realize that there is rarely a situation in which one strategy (ie, standardized pre-exercise stress testing) fits all; rather, one must "choose wisely" when referring asymptomatic patients for clinical exercise stress testing.

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