Impediments to clinical application of exercise interventions in the treatment of cardiometabolic disease

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Before enlightenment, chop wood, carry water.
After enlightenment, chop wood, carry water.
Zen proverb

Statins have become a pharmacologic cornerstone for the prevention and treatment of cardiovascular disease (CVD). However, it is clear from the large statin trials that maximal lowering of low-density lipoprotein cholesterol (LDL-C) levels still allows 2 out of 3 cardiovascular events to occur.[1] These events represent the so-called residual risk that remains after optimized statin therapy. Attempts to further lower LDL-C levels in patients with established CVD using high-dose statins,[2] adding ezetimibe,[3] or adding proprotein convertase subtilisin-kexin type 9 inhibitors[4,5] have each resulted in a further modest absolute event reduction of 1% to 2% over 2 to 6 years. None of these augmentation trials has shown a reduction in all-cause mortality.

The prevalence of obesity has continued to increase in Canada[6] and the United States.[7] There is concern that since 1990 the mortality benefits from control of smoking, hypertension, and lipid levels have been offset by the harmful cardiometabolic effects of obesity.[7] These effects are associated with hyperinsulinemia, diabetes, and metabolic syndrome. Many people with obesity exhibit the profile of "atherogenic dyslipidemia," which is characterized by high triglyceride levels, low or dysfunctional high-density lipoprotein (HDL) levels, and a predominance of small dense LDL particles.[8] The serum can contain large quantities of intensely atherogenic particles such as very low density lipoprotein, intermediate-density lipoprotein, chylomicron remnants, and remnant lipoproteins.[9] Attempts to reduce cardiovascular events by lowering triglyceride levels and raising HDL levels using niacin[10] or fenofibrate[11] in addition to statins have been ineffective in large randomized trials. Similarly, the addition of cholesterol ester transfer protein inhibitors to statins in high-risk patients has statistically significantly raised HDL levels, but has not resulted in event reduction.[12,13]

As we seem to have reached maximum therapeutic potential in terms of statin use, and as add-on drug therapy currently affords only modest additional benefit, it seems prudent to refocus our emphasis on lifestyle options that can provide event reduction in conjunction with statin therapy. There has been great success with smoking cessation.[14] Dietary and physical activity (PA) interventions can be similarly effective (*physical activity* is defined in **Box 1**[15,16]). Suboptimal implementation of effective PA interventions might reflect poor physician uptake as much as patient nonadherence, and the reasons for this will be explored further in this article.

Evidence for statins and PA

While statin benefits are well established, it might be less appreciated that PA is equally effective in preventing CVD mortality in secondary prevention[17] and could actually be superior in CVD and all-cause mortality reduction in primary prevention (**Table 1**)[3,17-57]; however, the level of evidence for PA interventions is less robust. **Table 1**[3,17-57] summarizes meta-analyses and salient randomized controlled trials (RCTs) evaluating benefits of statins and PA. There is, for example, good evidence that diabetes is increased in statin users,[32,33] while PA is a very effective preventive measure.[34,35] Similarly, obesity is higher in statin users,[36] while PA is an aid in prevention of weight gain.[37] Lower incidence of all cancers except melanoma is directly associated with PA,[44,45] as is a reduction in falls,[48,49] while statins have no such effect.[47] Quality of life, a key objective of health interventions, is uniformly improved with PA.[55-57] This outcome exists independent of sex and many chronic disease states, including cancer.[58] No useful data are available for the influence of statins on quality of life.

Box 1. Glossary of terms

Cardiovascular fitness: Attributes that enhance ability to perform PA. Measured by maximal oxygen uptake. Might be partially genetic in origin, but can be trainable with exercise[15]

Exercise: A subset of PA that has a conditioning or maintenance objective, and that is planned, structured, and repetitive[16]

MET: 1 MET is defined as 1 kcal/kg per hour and is roughly the energy equivalent expended by an individual at rest

PA: Body movement produced by skeletal muscle requiring energy expenditure. Might include occupational, recreational, and conditioning activities, as well as activities of daily living

METs—metabolic equivalents, PA—physical activity.

Table 1. Meta-analyses and RCTs evaluating effects of statins and PA on health outcomes

HEALTH OUTCOMES	FINDINGS WITH STATIN TREATMENT	COMMENTS	FINDINGS WITH PA	COMMENTS
CVD events	• Reduced in primary prevention (HR = 0.81)[18]	• Further 16% reduction in remaining RR using high-dose statins[3]	• HR of 0.69 comparing highest with lowest walking categories[19] • HR of 0.88 for moderate activity and -0.73 for vigorous activity[20] • In those with high levels of exercise, HR of 0.76 in men and -0.73 in women[21]	• Demonstrated dose response • Benefits at least equal to statin use and a good alternative if statins are not desired or tolerated[22*,23*]
CVD and all-cause mortality	• Reduced in primary prevention (HR = 0.86)[24] • Reduced in secondary prevention (HR = 0.82)[17]	• All meta-analyses found that all-cause mortality reduction was NS or lower than event reduction[18,24-29]	• Self report: HR of 0.70 for CVD mortality[30] • Fitness testing: HR of 0.43 for CVD mortality[30] • Accelerometry: HR of 0.60 to 0.37 for CVD mortality[31]	• Dramatic mortality reduction if a measure of fitness is used in place of self-report • Benefits for reduction in all-cause mortality and CVD events are much the same[19]
Diabetes risk	• Increased HR of 1.09; absolute risk increase of 0.4% (NNH = 225)[32] • High dose vs moderate dose increased HR to 1.12; absolute risk increase of 0.2% (NNH = 498). HR reduced for CVD events at 0.84[33]	• Risk of causing diabetes is very low but can become statistically significant when large numbers of people are taking treatment. Small further increase in risk at high dose	• Reduced HR of 0.74 at the recommended exercise level, 0.64 at double the recommended exercise level, and 0.47 at higher exercise levels[34]	• Only 1 meta-analysis is available • Moderate exercise at about 18 km/wk was found to be equal to combined diet, exercise, and weight loss for diabetes prevention in the STRRIDE study[35*]
Obesity	• For those who used statins for > 10 y, BMI increased by 1.3 kg/m^2, while for nonusers BMI increased by 0.4 kg/m^2. Statin users consumed statistically significantly more calories and fat[36*]	• This was a repeated cross-sectional study done at 10-y intervals using NHANES data, which involved following 28 000 people. Large potential for confounding[36]	• Moderate- to high-intensity exercise done 3 to 5 times a wk can produce a 2% to 3% weight loss over 6 mo[37]	• These findings are the results of a review of RCTs and meta-analyses. Data are very heterogeneous, making appropriateness of meta-analysis questionable
Cognition	• No evidence from recent Cochrane meta-analyses for benefit of statins in treatment[38] or prevention[39] of Alzheimer dementia • No studies evaluating effect on vascular dementia	• Studies found no evidence for benefit or harm when statins were given to patients with dementia. All were RCTs of short duration	• HR of 0.65 for cognitive decline and 0.86 for dementia in meta-analysis of prospective cohort studies[40] • No evidence for benefit in Cochrane meta-analysis of RCTs[41]	• RCTs were not blinded, and all interventions were < 1 y. Prospective cohorts had much longer follow-up • Both studies acknowledge potential for bias • Weak evidence for benefit
Cancer risk	• Meta-analysis of statin RCTs showed no benefit or harm[42] • No influence of statins on cancer mortality in long-term follow-up of RCTs at 6 to 14 y[43]	• Long-term follow-up studies were no longer randomized	• HR of 0.93 to 0.84 for reduction in highest vs lowest activity levels[44,45]	• Meta-analyses of prospective cohort studies, therefore association only • All cancers were reduced in incidence except melanoma, which was increased[44]

Table 1 *continued on page 166*

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HEALTH OUTCOMES	FINDINGS WITH STATIN TREATMENT	COMMENTS	FINDINGS WITH PA	COMMENTS
Fall risk	• Inconsistent results from prospective cohort studies: -no increased risk and no proximal weakness[46]* -increased fall risk with increased proximal muscle weakness[47]*	• No available meta-analyses	• Meta-analyses of prospective cohort studies suggest risk reduction with rate ratios of 0.71[48] to 0.63[49]	• Clear benefit despite increased activity levels. Subject to confounding and can only imply association
Fracture risk	• Meta-analysis of case-control and cohort studies shows association with reduced fracture risk (OR = 0.80)[50]	• No available RCTs	• Meta-analysis of RCTs reporting exercise interventions shows a rate ratio of 0.60 • Meta-analysis of cohort studies suggests association with reduced falls (RR = 0.71)[51]	• Findings from secondary analysis of RCTs and cohort studies. Causation not firmly established
Elderly	• Mortality: No mortality reduction in primary prevention for those aged > 65 y over 3-y follow-up[52] • Mortality: HR of 0.78 in secondary prevention for those aged > 65 y over 5 y[53]	• However, statistically significant CVD event reduction is shown for both primary and secondary prevention in these studies	• Self-report: Mortality reduced for those aged > 65 y who achieved recommended PA level (HR = 0.72) and for those who engaged in higher-than-recommended PA levels (HR = 0.65)[54] • Fitness testing: HR of 0.71 to 0.46 for recommended vs high PA levels among those aged > 70 y[23]*	• Benefit in the elderly similar to younger age groups with direct dose response
QOL	• No data	• Statin trials have consistently failed to report influence on QOL[24]	• Improved QOL from exercise-based cardiac rehabilitation on meta-analysis of RCTs[55] • Similar improvements with exercise in 2 RCTs: in women showing a dose response[56]*; improved QOL in 9-mo trial in those with diabetes[57]*	• Numerous RCTs of exercise in various chronic disease states also demonstrate beneficial effects of exercise on QOL

BMI—body mass index, CVD—cardiovascular disease, HR—hazard ratio, NHANES—National Health and Nutrition Examination Survey, NNH—number needed to harm, NS—non-significant, OR—odds ratio, PA—physical activity, QOL—quality of life, RCT—randomized controlled trial, RR—relative risk, STRRIDE—Studies of a Targeted Risk Reduction Intervention through Defined Exercise.
*Denotes RCT with statistically significant outcomes.

Suboptimal implementation

There are several possible reasons for suboptimal implementation of exercise interventions.

Reliance on inappropriate surrogate markers of success

Lipoprotein changes: Triglyceride levels fall reliably with exercise and levels are reduced for up to 15 days following a period of activity.[35] High-density lipoprotein cholesterol level is increased, but this occurs primarily in those who exercise the most.[59] Total cholesterol and LDL-C levels are generally unchanged with PA in available meta-analyses of RCTs.[60-63] Included trials tend to have a duration of 1 to 6 months on average. It has been shown that short-term variability in cholesterol levels might vary by about -0.80 mmol/L to 0.80 mmol/L, and that it might take up to 4 years for long-term variation to exceed short-term variability.[64] True benefits of PA are therefore unlikely to be reflected in the standard lipid profile over the short term. Benefits might instead be mediated by a reduction in LDL particle number as reflected by apolipoprotein B values[65] or by direct measurement,[66] making diffusion of atherogenic particles across the vascular endothelium less likely. Reliance on changes in LDL-C and total cholesterol levels will not reinforce the use of PA as a beneficial intervention.

Weight change: While the recommendation of engaging in moderate exercise for 30 minutes for 5 days a week plus 2 days of resistance training is effective in preserving cardiometabolic health,[67] it is insufficient to prevent ongoing weight gain over time. Prevention of transition to overweight or obese status in our current food environment requires exercising for 45 to 60 minutes a day,[68] and weight loss would require even more time if exercise alone were the intervention. Improved cardiometabolic health through exercise can be achieved without weight loss.[69,70] It seems more reasonable to regularly monitor any changes in activity behaviour patterns as a measure of PA adherence, rather than to have a weight-loss expectation.

Reliance on short-term RCTs for information on long-term outcomes. There are no long-term RCTs that establish the causal effect of PA on CVD incidence.[60] Ethical and feasibility issues make group assignment and adherence impossible to initiate and maintain. In fact, different studies are necessary to differentiate the efficacy and effectiveness of an intervention.[71] Randomized controlled trials address efficacy and establish what we might expect. Effectiveness under real-world conditions requires an observational study, preferably a pragmatic controlled trial, with follow-up of study cohorts over time.[72] It is difficult to enforce randomization in a preference-dominated world for sufficiently long periods of time.[71] The most informative PA studies are prospective cohorts that are followed long enough to detect potential adverse effects and that stratify participants to be compared according to baseline risk, controlling as best as possible for confounding. Strength of association is also enhanced if a number of the Bradford Hill criteria[73,74] for establishment of causality are met (**Table 2**).[15,19,23,31,73-79] Randomized controlled trials cannot properly evaluate benefits and adverse effects over time while addressing patient preference and ensuring adherence under real-world conditions.

Concern over nonadherence. No studies were found on documenting adherence to an exercise prescription over time. A 2-year prospective study found that 18% to 24% of adults maintained recommended PA levels over the entire period.[80] These subjects were self-motivated and received no prescription. On the other hand, 2-year adherence to statin medication was 40% following acute coronary syndrome, but only 25% for primary prevention.[81] It seems likely that if activity interventions were reinforced as often and as enthusiastically as drug interventions, uptake and adherence might be similar to statin therapy. Small changes in activity produce large gains. Going from a sedentary state to a low level of any activity is associated with the highest incremental cardiometabolic benefit.[82] Interventions far short of current recommendations can still have a considerable effect on cardiovascular outcomes.[83]

Failure to address diet. Excessive caloric and simple carbohydrate intake will completely overwhelm the weight-moderating effects of PA.[84] Physical activity can aid weight control, and beneficial cardiometabolic effects will occur without weight loss, but there must be control of excess caloric and simple carbohydrate intake in our obesogenic environment if the usual default weight gain is to be avoided over time.[85,86] The Mediterranean eating pattern is the best alternative for avoidance of weight gain,[87] with no weight increase shown over 5 years despite unrestricted caloric intake in a large RCT.[88]

Insufficient knowledge to provide an appropriate prescription. Physicians' lack of knowledge or confidence in generating an exercise prescription (**Box 2**)

Table 2. Bradford Hill criteria for assessing the causal nature of an observed association

BRADFORD HILL CRITERIA	EXPLANATION	EXAMPLE
Strength of association	Strong associations are most likely to be causal	High PA confirmed by accelerometry associated with 40% to 63% reduction in all-cause mortality[31]
Consistency of association	Similar outcomes in different populations and in studies that might be prospective or retrospective	Higher fitness associated with reduced all-cause mortality in large prospective[23] and retrospective[75] cohort studies
Specificity of association	If an association is greatly increased in a specific group exposed to an intervention, the case for causation is strengthened	In a large cross-sectional study, cardiorespiratory fitness was strongly associated with reduced waist circumference and metabolic syndrome[15]
Temporality	A necessary criterion. Exposure must precede outcome	All prospective cohort studies show benefit of PA in event and mortality reduction
Biologic gradient	Causal association is more likely if a dose response is demonstrable	Walking at higher volume or intensity associated with progressive reduction in CVD events and all-cause mortality[19]
Plausibility	Compatible with current knowledge. Not always a necessary criterion, as this knowledge might be new	Occupational energy expenditure has dropped by 140 calories per day since the 1960s. This might be a contributing factor to increased obesity[76]
Coherence	Observed outcome should be congruent with other known characteristics of disease biology or natural history	PA prevents oxidative stress, reduces inflammation, and improves endothelial function[77]
Experiment	Occasionally causation can be demonstrated by a controlled intervention in a clinical trial	Exercise intervention superior to PCI for event-free survival in randomized single-blind trial over 12 mo[78]
Analogy	Probably the weakest argument for association, but worth consideration if the outcome is adverse	Resistance training has similar benefits for glycemic control to aerobic training[79]

CVD—cardiovascular disease, PA—physical activity, PCI—percutaneous coronary intervention.
Data from Lucas and McMichael[73] and Hill.[74]

is a reflection of the fact that our teaching lacks the conviction that PA can be an effective health intervention. We therefore rely upon drugs, which are inferior to PA in many ways, including in mortality reduction and improvement in quality of life. The exercise prescription should be tailored for the individual patient considering baseline status, available time, and desired outcome. Brief interventions regularly reinforced have been shown by some to be effective.[89,90] A sample prescription form can be found at **www.exerciseismedicine.org/canada/assets/page_documents/EIMC_Pad_ENnewlogo_v3.0_1_copy.pdf**. **Table 3**[56,67,68,83,89,91-100] presents illustrative exercise intervention scenarios for different patient needs.

Box 2. Strategies that might help reinforce an increase in PA

When trying to increase a patient's PA levels ...

- Be an enthusiastic and committed prescriber with confidence in the evidence
- Pay attention to objective measures of behaviour change rather than to unhelpful surrogates as measures of success
- Consider suggesting dietary modification and simple carbohydrate reduction to avoid hyperinsulinemia and avoid default weight gain
- Have confidence in generating an appropriate exercise prescription for every sedentary patient
- Be willing to reinforce an exercise prescription with a program referral or a brief intervention at every visit
- Recognize that we must not rely only upon pharmacotherapy to improve QOL and longevity

PA—physical activity, QOL—quality of life.

Cardiorespiratory fitness, a measurable outcome of increased PA, is one of the strongest prognostic indicators for long-term survival, surpassed only by patient age.[75] The combination of increased fitness and statin therapy is additive when examined in long-term retrospective[75] and prospective[23] cohorts. Most older adults can achieve an exercise capacity of 5 to 7 metabolic equivalents (METs), which confers the same protection as a statin given to unfit subjects with an exercise capacity of less than 5 METs (**Box 1**)[15,16]; however, adding a statin at this level of fitness produces a further 35% relative risk reduction.[23] Generally, an improvement in exercise capacity of 1 MET confers a mortality risk reduction of 12% to 15% according to meta-analysis.[101]

Statins added to PA might expose the patient to increased myopathy risk, especially at the extremes of

Table 3. Illustrative exercise interventions for varying patient needs

PATIENT PRIORITY	INTERVENTION	COMMENT
No motivation to increase activity	Ask or seek permission to discuss reduction of sedentary behaviour. If permission granted, proceed with the 5 *As* framework[91,92]	This model has been used in smoking[91] and obesity[92] management. Repeated brief simple advice can increase adoption[89,91]
Motivated but highly unfit	Use pedometer or accelerometer to evaluate number of steps per d at baseline. Consider initially adding 1000 to 2000 free-living steps per d	<5000 steps per d considered sedentary. Marked benefit appears at low levels of PA increase. Some increase in activity is better than none[93]
Motivated but wishes to do the minimum for benefit	Slow running[94] for 5 to 10 min per d or brisk walking[83] for 15 min per d can reduce mortality 14% over 8 y and 30% over 15 y, respectively	These activity levels are approximately half of current exercise recommendations
Motivated, but no time (has 2 minimum wage jobs)	Use a pedometer or accelerometer to evaluate number of steps per d at baseline. Try to increase free-living steps by 2000 steps per d by increasing mobility options	Pedometers are inexpensive. Mobility options could include walking to work, using stairs, and walking during lunch breaks
Motivated to optimize cardiometabolic risk	30 min of moderate PA 5 d per wk, ≥75 min of vigorous PA per wk, or a combination of moderate and vigorous PA; plus 2 d of resistance training per wk[67]	This level of exercise is insufficient to prevent weight gain.[68] CVD risk reduction increases at higher exercise levels with diminishing effectiveness at 6 to 10 times the recommended levels[95,96]
Wishes to avoid gaining further weight	Requires 45 to 60 min of moderate PA per d.[68] Slowing of weight gain unlikely to happen without dietary modification as well	7000 steps per d is associated with energy balance and minimal weight gain.[97] Mediterranean diet is not associated with weight gain[98]
Motivation includes wish to lose weight	Would require >250 min per wk of moderate exercise if used alone and dietary intake not excessive[99]	This exercise level and dietary modification would have to be maintained in order to avoid weight regain[99]
Lifelong runner (10 km 3 times per wk at 10 km per h)	More-than-adequate exercise level for health maintenance and mortality reduction. Chosen exercise level should maximize QOL for the individual[56]	Exercise produces benefit up to 10 times the recommended levels with diminishing returns on mortality reduction.[96] There might be loss of benefit at very high levels[100]

CVD—cardiovascular disease, PA—physical activity, QOL—quality of life.

drug and activity dosing, and in the elderly.[102] The exercise prescription should precede the statin prescription, and an optimized PA program should be in place before adding drug therapy.[103,104]

Conclusion

Atherosclerosis is a lifestyle problem and deserves a lifestyle solution, especially in primary prevention.[105] Strategies outlined in **Box 2** might help reinforce an increase in PA.

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Competing interests
None declared

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