MAYO CLINIC

Impact of Statins on Physical Activity and Fitness: Ally or Adversary?

See also page 1338

Statin drugs, in my view, are the best cardiovascular drugs ever created, in that they have the greatest potential to prevent atherosclerotic plaques and their complications, and they also have the greatest potential to arrest plaque formation, and therefore, to prevent additional atherosclerotic events. The statin drugs are to atherosclerosis what penicillin was to infectious diseases.

—William C. Roberts[1]

Since their introduction nearly 3 decades ago, statins (ie, 3-hydroxy-3-methylglutaryclo enzyme A reductase inhibitor drugs) have become widely prescribed in the primary and secondary prevention of cardiovascular (CV) disease (CVD) because of their favorable impact on lipid/lipoprotein metabolism and patient survival.[2] Recent randomized controlled trials and meta-analyses[2-4] have reported 20% to 44% reductions in cardiac events after the initiation of statin therapy, with comparable cardioprotective benefits for men and women. Despite the salutary effects, there are some unintended consequences of statins, including being linked to muscle pain, cramps, and fatigue, which may lead to reduced levels of physical activity (PA) and/or structured aerobic exercise. Moreover, statins have been associated with a higher incidence of diabetes mellitus (DM),[5] elevation in serum creatine kinase concentrations (a widely used biomarker of muscle tissue injury), liver dysfunction, inflammation, and myopathy,[6-8] as well as attenuated training-induced increases in cardiorespiratory fitness (CRF) levels.[9] Reductions in PA and/or CRF levels—whether drug related or not—are particularly troubling, in view of their strong inverse relation with CV and all-cause mortality,[10] and the fact that structured aerobic exercise and the positive aspects of drug therapy appear to offer similar mortality reductions in the secondary prevention of coronary heart disease (CHD).[11]

In this issue of *Mayo Clinic Proceedings*, Williams and Thompson[12] provide an insightful epidemiological report on these aforementioned issues by evaluating a large cohort of physically active individuals who were diagnosed with hypercholesterolemia and whether a potential decrease in the level or intensity of exercise was greater in those treated with statins than in those who were not.

To clarify the impact of statin therapy on levels of habitual PA, the investigators used the well-established National Runners' and Walkers' Health Study database, the largest epidemiological cohort specifically created to assess the health outcomes associated with long-term participation in moderate-to-vigorous exercise regimens (ie, walking or running) in men and women with and without CVD, including CHD. The study population included 66,377 runners and 12,031 walkers not using cholesterol medications at baseline, who were initially surveyed and resurveyed over a mean follow-up of 7.2±1.7 years.[12] The standardized survey questionnaires included extensive queries on (1) exercise practices; (2) whether study participants used specific medications to treat high cholesterol levels, hypertension, or DM; and (3) whether they developed "incident hypercholesterolemia" during follow-up, defined as initiating drug therapy for the condition or self-reported physician diagnosis of high cholesterol levels. Additional questions included demographic information (eg, age, sex, height, and weight), smoking status, dietary practices, alcohol consumption, and comorbid conditions, including a history of CHD.

The investigators found that statins per se were not associated with a reduced exercise level or intensity (which Williams and Thompson[12] suggest is good news for patients and the physicians who counsel them). Specifically, among individuals who were diagnosed with hypercholesterolemia, and with the passage of time, exercise levels decreased comparably in patients in whom statins were and were not used. These intriguing results raise the potential for reverse causality; that is, a decrease in exercise levels potentially resulted in adverse physiological and

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TABLE. Interactive Effects of Physical Activity, Cardiorespiratory Fitness, and Statin Treatment in Young, Middle-Aged, and Older Adults

Reference, year	Population	Age (y)	Study design	Major findings
Sinzinger and O'Grady,[13] 2004	22 highly trained athletes with FH	13-35	Descriptive/observational	~20% of professional athletes with FH tolerate statin treatment without adverse effects.
Traustadóttir et al,[14] 2008	9 men, 1 woman with LDL-C levels >3.3 mmol/L (130 mg/dL)	55-76	Descriptive/observational	After 12 wk of simvastatin treatment (80 mg/d), no significant changes were observed in $\dot{V}o_2$max, endurance, or measures of muscle function.
Parker et al,[15] 2013	420 healthy, statin-naive men and women	41-47	RCT; atorvastatin (80 mg/d) vs placebo	After 6 mo, there was no adverse effect of atorvastatin on muscle strength or exercise capacity; however, increased myalgia and CK levels were noted.
Mikus et al,[9] 2013	37 inactive, overweight/obese adults with ≥2 MS risk factors	25-59	RCT; exercise vs exercise plus statins	$\dot{V}o_2$max increased 10% in the exercise-only group, but only 1.5% in the exercise-plus-simvastatin group. Similarly, SMCSA increased, respectively, by 13% and decreased by 4.5% in these groups.
Kokkinos et al,[16] 2013	10,043 veterans with dyslipidemia	59±11	Descriptive/observational	Statin treatment and increased CRF are independently associated with lower mortality in veterans with dyslipidemia (see Figure 2).
Lee et al,[17] 2014	5994 participants in the Osteoporotic Fractures in Men Study	≥65	Descriptive/observational	Over a 6.9-y follow-up, men receiving statins engaged in modestly less moderate and vigorous physical activity (~10%) and more sedentary behavior.
Rengo et al,[18] 2014	1201 patients undergoing exercise-based cardiac rehabilitation	65±11	Descriptive/observational	Improvements in $\dot{V}o_2$peak were 3.2 and 3.1 mL/kg per minute for statin users and nonusers, respectively. Long-term statin use does not attenuate aerobic training effects.
Terpak et al,[19] 2015	749 adult masters swimmers and 558 controls	≥35	Descriptive/observational (survey, self-reported)	Statin use was not associated with decreased self-reported swimming performance, considering the frequency, duration, or intensity of workouts.
Qureshi et al,[20] 2015	17,264 participants in the FIT Project	59±8	Descriptive/observational	Statin use was not significantly associated with lower peak METs in this large multiracial cohort of men and women.
Panza et al,[21] 2015	418 statin-naive adults	44±16	RCT; atorvastatin vs placebo	Sedentary time increased and physical activity decreased in the total study population during 6 mo of drug treatment, independent of group assignment.
Williams and Thompson,[12] 2015	66,377 runners and 12,031 walkers in the NRWHS	~21-82	Descriptive/observational (survey, self-reported)	Decreased exercise activity occurred similarly in runners and walkers who developed hypercholesterolemia, irrespective of statin treatment.

CK = creatine kinase; CRF = cardiorespiratory fitness; FH = familial hypercholesterolemia; FIT = Henry Ford Exercise Testing Project; LDL-C = low-density lipoprotein cholesterol; MET = metabolic equivalent (1 MET = 3.5 mL/kg per minute); MS = metabolic syndrome; NRWHS = National Runners' and Walkers' Health Study; RCT = randomized controlled trial; SMCSA = skeletal muscle citrate synthase activity; $\dot{V}o_2$max = maximal oxygen consumption; $\dot{V}o_2$peak = peak oxygen consumption.

clinical responses, including hypercholesterolemia, which prompted the initiation of statin therapy, rather than statin therapy reducing the level of habitual PA.

Limitations of the observational study included analyses that were based on self-reported survey data and the fact that most participants were taking low-dose statins, which may have been less likely to adversely impact their walking and running regimens. Other potential confounding variables include the adherence to, or the duration of statin use, and intercurrent illness or injury.

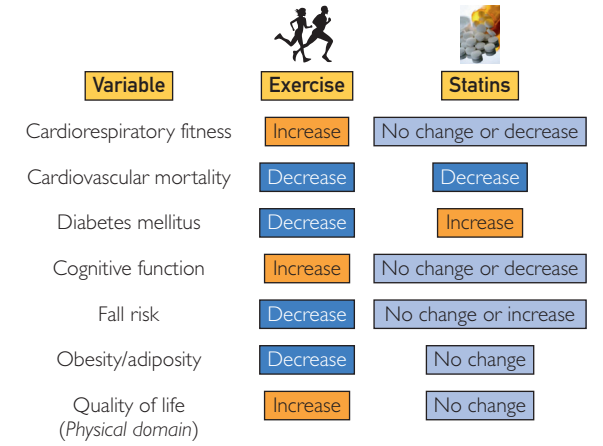

FIGURE 1. Comparison of the effects of exercise training and statins on varied risk factors and health outcome modulators in the prevention of initial and recurrent cardiovascular events. Although both regular exercise and statins appear to confer substantial reductions in cardiovascular mortality, there are numerous independent and additive benefits of exercise over statins when other variables are considered.[29]

IMPACT OF STATINS ON PA AND CRF

Over the past decade, 11 relevant observational studies and randomized controlled trials[9,12-21] (as summarized in the Table) evaluated the interactive effects of PA (including the types of training regimens, lifestyle activity, or both), CRF, and statin use in young, middle-aged, and older adults. According to one report,[13] only 20% of 22 highly trained athletes with familial hypercholesterolemia were able to tolerate any of the 5 statins then available. In another observational study, Lee et al[17] noted that PA declined more in older men (age, ≥65 years) who had recently initiated statin therapy than in statin nonusers. Over the follow-up period, older men receiving statins engaged in modestly less moderate and less vigorous PA and had more sedentary behavior. However, the generalizability of these population-specific observational findings—which were further limited by recall bias, short-duration accelerometer data collection, and the inability to account for numerous potential confounding variables—is tenuous at best.

Of the remaining 9 studies reviewed, 3 reported that statin use per se was unrelated to habitual PA[12,19,21]; 2 found that statins were not associated with lower exercise capacity, expressed as peak metabolic equivalents (METs), or impaired exercise trainability[18,20]; and an additional 2 noted that statins were unrelated to changes in muscle strength or exercise capacity.[14,15] In contrast, Mikus et al[9] randomized sedentary overweight or obese adults (n=37) with 2 or more metabolic syndrome risk factors to 12 weeks of supervised aerobic exercise training alone (n=19) or in combination with 40 mg/d of simvastatin (n=18). CRF levels increased by 10% ($P<.05$) with training in the exercise-only group, but only 1.5% in the exercise-plus-simvastatin group ($P<.005$ for group-by-time interaction). Citrate synthase activity, a measure of skeletal muscle mitochondrial content, increased by 13% in the exercise-only group ($P<.05$), but decreased by 4.5% in the exercise-plus-statin group ($P<.05$ for group-by-time interaction). The investigators concluded that statins (or at least simvastatin, which potentially has the propensity for more muscle adverse effects than do other statins) attenuate exercise training–associated adaptations in patients at risk for the metabolic syndrome, signified by reduced improvement in CRF levels and contrasting citrate synthase responses. Elsewhere, Kokkinos et al[16] reported that statin treatment and increased CRF levels, when combined, provided independent and additive survival benefits in military veterans with dyslipidemia. The discrepancy between clinical trial evidence and selected epidemiological associations may have been due to the lack of a placebo-treated or control group in some studies.[21]

EXERCISE PLUS STATINS: A SYNERGISTIC COMBINATION?

If the current mantra "exercise is medicine" is embraced, the mortality benefits of prescribed PA should be comparable to those of commonly prescribed cardioprotective medications, and under- and overdosing are possible.[22] In men and women with and without CHD, each 1-MET increase in CRF levels is associated with an approximately 15% reduction in CV mortality, which, in the post–myocardial infarction population, compares favorably with the survival benefit conferred by low-dose aspirin, statins, β-adrenergic blockers, and angiotensin-converting enzyme inhibitors.[23,24] Another review of prospective cohort studies and

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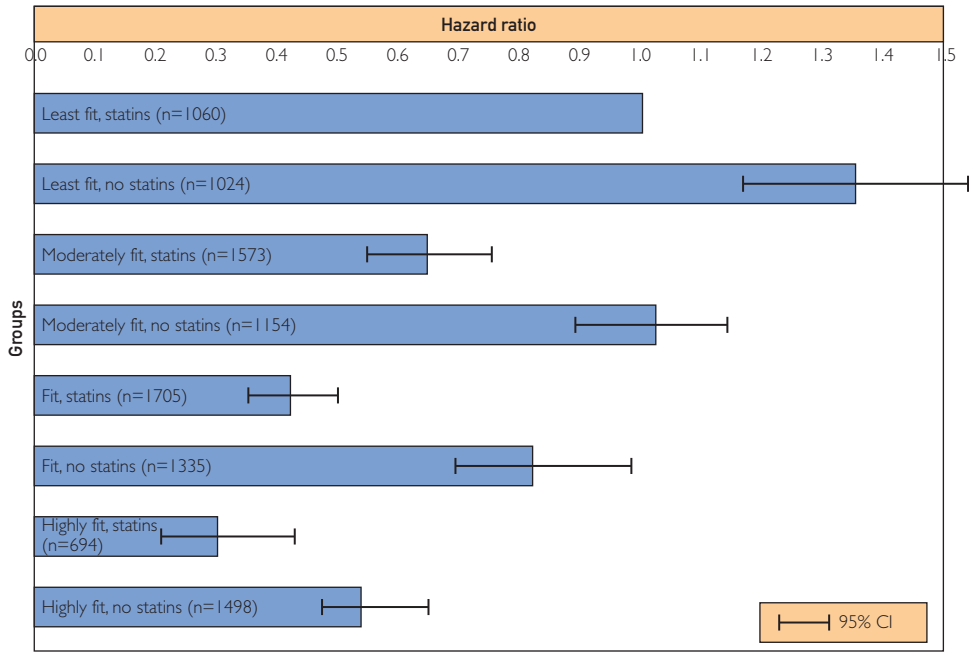

FIGURE 2. Mortality risk, expressed as fully adjusted hazard ratios and 95% CIs, for combined cardiorespiratory fitness and statin categories. Patients with a peak MET value of 5.0 or less were classified as "least fit"; those with a peak MET value of 5.1 to 7.0 were classified as "moderately fit"; those with a peak MET value of 7.1 to 9.0 were classified as "fit"; and those with a peak MET value greater than 9.0 were classified as "highly fit."[16]

randomized controlled trials in patients with established CHD sought to provide evidence for a prognostic benefit of lifestyle modification, including structured exercise. Effect estimates for higher levels of PA approximated a 25% lower risk of all-cause mortality.[25] Moreover, a recent meta-analysis[11] that included 305 randomized controlled trials and 339,274 participants reported comparable survival benefits of exercise treatment vs drug interventions in the secondary prevention of CHD. In patients with stroke, exercise interventions were more effective than drug treatment.

As compared with the Adult Treatment Panel III guidelines,[26] implementation of the 2013 American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol[27] would increase the number of US adults who would be eligible for statin treatment by 12.8 million, with the greatest increase in adults between the ages of 60 and 75 years without CVD.[28] These new guidelines[27] make recommendations about the appropriate statin therapy to reduce low-density lipoprotein cholesterol (LDL-C) levels in the following patient subsets:

1. patients with clinical CHD;
2. patients with LDL-C level of greater than 190 mg/dL (to convert mg/dL values to mmol/L, multiply by 0.0259), such as those with familial hypercholesterolemia;
3. patients with DM who are 40 to 75 years of age with LDL-C levels between 70 and 189 mg/dL and without evidence of CHD; and
4. patients without evidence of CHD or DM who are 40 and 75 years of age with LDL-C levels between 70 and 190 mg/dL and a 10-year CHD risk of more than 7.5%.

Exercising regularly appears to have CV mortality benefits that are similar to those of statin therapy, but with other salutary effects (Figure 1).[29] For example, statins tend to increase the incidence of DM,[5] whereas regular moderate-to-vigorous exercise appears to reduce the incidence of DM by a similar magnitude. An increase in PA levels also improves insulin action in obesity, with or

without a concomitant reduction in body weight and fat stores.[30] This is an important (and often overlooked) salutary effect, suggesting that PA is as efficacious in preventing insulin resistance as losing body weight. In addition, long-term exercise has been shown to improve CRF levels or exercise capacity; enhance cognition; reduce fall risk, body weight, and fat stores; and improve quality of life—all of which have relevance to improved health outcomes.[29] In contrast, statins have little or no effect on these variables.[29]

Although both higher CRF levels and statin use are effective in reducing CVD risk, until recently few data were available on the impact of these combined interventions on all-cause mortality. To address this question, Kokkinos et al[16] studied 10,043 veterans who had hypercholesterolemia (mean age, 59±11 years) and who underwent exercise testing to determine CRF levels. During a mean follow-up of 10 years, 2318 patients died. Mortality risk was higher in those veterans not taking statins (28% vs 19%). In patients who took statins, mortality risk decreased as CRF levels increased: that is, highly fit individuals (>9 METs) who were taking statins had a 70% lower mortality rate than did the least fit cohort (≤5 METs) who were taking statins. For those not taking statins, the hazard ratio for the least fit participants was 1.35 (95% CI, 1.17-1.54) and it progressively decreased to 0.53 (95%CI, 0.44-0.65) for those in the highest CRF quartile (Figure 2). In a recent subgroup analysis of these data,[29] researchers found that among veterans in the highest quintile of CRF (>10 METs), the marked reduction in mortality (when compared to unfit individuals) was similar regardless of whether statins were taken or not. These findings suggest that middle-aged and older adults who can achieve more than 10 METs during exercise testing (implying the partial or complete attainment of stage IV [or higher] on the Bruce treadmill protocol or the ability to run at a 6 mph pace or faster) receive little or no additional benefit from taking statins for CHD prevention.

In summary, the report by Williams and Thompson[12] in this issue of *Mayo Clinic Proceedings* extends previous studies suggesting that prescribed statins, especially in low-to-moderate doses, do not reduce habitual PA or exercise intensities, at least in any meaningful, clinically important way. With 2 exceptions (see the Table),[9,17] statins were not associated with reduced PA levels, peak METs, or measures of muscular strength, nor were they associated with impaired exercise trainability. These data and other recent reports[10] strongly support the independent and additive benefits of both improved CRF levels *and* statin therapy on reducing all-cause mortality.[16] The high prevalence of statin use in the United States and the new guidelines[27] emphasizing more aggressive treatment for more people with higher doses of statins suggest the need for closer monitoring of their potential adverse effects.

"We doctors can now state from our experience with people, both sick and well, and from a growing series of scientific researches that 'keeping fit' does pay richly in dividends of health and longevity." Like all statements of wisdom, this observation, by the late Dr Paul Dudley White,[31,p429] is both elegant and reasoned, and so clearly evident and acceptable today that we feel we should have known it all along. When combined with statin therapy, CRF can provide a powerful survival advantage to the patients we counsel.

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