Statin Therapy Does Not Attenuate Exercise Training Response in Cardiac Rehabilitation

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To the Editor

HMG co-reductase inhibitors (statins) lower cardiovascular events in patients with coronary heart disease (CHD). Beyond lipid effects, statins provide benefits through effects on inflammation, the renin-angiotensin system, endothelial function, and arterial compliance. However, statin use is associated with myalgia and fatigue. Furthermore, Mikus et al. (1) reported that simvastatin attenuated aerobic training in statin-naïve, overweight subjects at risk for metabolic syndrome during a 12-week exercise program similar to that used in cardiac rehabilitation (CR). This finding is concerning for CR populations, as baseline aerobic capacity (VO_{2peak}) and improvements after participation are correlated with reductions in cardiovascular disease–related and all-cause mortality (2). Additionally, exercise in conjunction with statin therapy lowers mortality in hyperlipidemic patients more than either therapy alone (3). Given the prevalence of statin treatment among patients undergoing CR, we sought to determine whether its use attenuates the exercise-training response, measured directly by VO_{2peak} (ml O_2/kg/min) in CR patients with CHD.

Study data were prospectively collected from January 1996 to July 2013 and included those from patients after an acute CHD event who performed both CR entry and exit exercise-tolerance tests with expired-gas analysis. The cohort was divided into two groups on the basis of statin use throughout the CR program. Each patient completed an exercise program of 3 sessions/week for 36 sessions.

Of 5,750 patients, 1,201 with CHD met study criteria over the review period, including 968 (81%) in the statin group and 233 (19%) in the nonstatin group. The percentage of patients taking statins over the study period increased from 56% during 1996–1998, to 80% throughout 2003–2005, and finally to 94% within 2010–2012 (p < 0.0001 for trend). Groups were similar by sex. The nonstatin group began CR later after hospital discharge, and had lower body weight, body mass index, VO_{2peak}, handgrip strength, and self-reported physical fitness, but higher depression scores. The statin group had significantly lower total

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cholesterol and low-density lipoprotein cholesterol levels, evincing adherence to the medication (Table 1). Smoking status and rates of type 2 diabetes mellitus did not differ.

Adherence to exercise training was similar between groups (mean ± SD: 26 ± 10 sessions vs. 26 ± 9 sessions; p = 0.97). VO_{2peak} increased similarly after exercise training in both study groups when expressed per body mass (p = 0.73) or in absolute terms (in l O_2/min) (p = 0.84) (Table 1). Furthermore, changes in handgrip strength, self-reported depression, and physical function scores were similar between groups.

For patients with a surgical diagnosis (coronary artery bypass grafting), 392 (76%) were taking statins versus 122 not taking statins. The increase in VO_{2peak} was similar in these two subgroups (mean ± SD: +4.0 ± 3.9 ml O_2/kg/min vs. +3.8 ± 3.6 ml O_2/kg/min; p = 0.74).

Within the statin group, men had a higher baseline VO_{2peak} (mean ± SD: 20.6 ± 6.6 ml O_2/kg/min vs. 15.6 ± 4.4 ml O_2/kg/min; p < 0.0001) and a greater increase with training (mean ± SD: 19.4 ± 21.8% vs. 13.1 ± 20.8%; p < 0.0001) compared with those in women, although differences were consistent across statin status (p = NS).

In view of a recent study documenting attenuated exercise training in overweight patients taking statin medications (1), we assessed whether statin use blunts exercise training in patients with CHD participating in CR. In contrast, our analysis demonstrates no effect of statins on the exercise-induced improvement in VO_{2peak} during CR. Furthermore, our results demonstrate an improved VO_{2peak} in the range of previously reported values. Because the exercise-training response to CR is linked to improvements in prognosis (2), our findings have relevance to >250,000 patients participating in CR annually in the United States.

The study by Mikus et al. (1) was limited by not comparing pre-training, on-statin exercise-test status to pre-statin status to assess the acute effect of statins on exercise performance prior to training. Therefore, their results may be explained by an acute reduction in VO_{2peak}, whereas both groups could have trained similarly. Additionally, Mikus et al. (1) did not include a placebo group (4).

The nonstatin group in our study consisted of 52% surgical patients versus 40% in the statin group. Although our data documented baseline differences by statin status in fitness, strength, physical function, and depression scores, the baseline differences were likely due to higher rates of surgical recovery in the nonstatin group versus the medically treated patients, not statin use per se. However, the primary goal of the study, to investigate training-induced improvements in fitness on or off statin treatment, is less in doubt, as the training response between groups was identical. Although the proportion of men to women differed between groups, this is consistent with national CR enrollment, and the effects of training in patients of both sexes receiving statin medications were within the range of previously reported values.

The primary strength of our study was the investigation of the effect of statin use on exercise-training adaptations, assessed by changes in VO_{2peak} directly measured by gas analysis rather than estimated by treadmill time, in a large cohort of CHD patients. Additionally, we analyzed multiple clinical variables, including baseline strength, fitness,

and body mass index. Limitations included nonrandomized analysis of predominantly Caucasian patients from a single clinical center. Second, data on underlying musculoskeletal conditions that might have affected exercise ability were not available. Third, we did not measure the acute effects of statin use. Finally, within the statin group, we did not have data to verify the type and dosage of medication, and the length of statin use ranged from 1 month to multiple years as we had data only on whether patients were taking or not taking a statin medication during the training period. Nonetheless, our results clearly demonstrate that long-term statin use does not attenuate aerobic training effects in CR patients and that the expected survival benefits of CR are expected, indeed, to persist.

Acknowledgments

References

1. Mikus CR, Boyle LJ, Borengasser SJ, et al. Simvastatin impairs exercise training adaptations. J Am Coll Cardiol. 2013; 62:709–14. [PubMed: 23583255]

2. Vanhees L, Fagard R, Thijs L, Amery A. Prognostic value of training-induced change in peak exercise capacity in patients with myocardial infarcts and patients with coronary bypass surgery. Am J Cardiol. 1995; 76:1014–9. [PubMed: 7484853]

3. Kokkinos PF, Faselis C, Myers J, Panagiotakos D, Doumas M. Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidemia: a cohort study. Lancet. 2013; 381:394–9. [PubMed: 23199849]

4. Thompson PD, Parker BA. Statins, exercise and exercise training. J Am Coll Cardiol. 2013; 62:715–6. [PubMed: 23583256]

Table 1

Clinical and Exercise Parameters in Cardiac Rehabilitation

	Statin Group (n = 968)	Nonstatin Group (n = 233)	p Value
Baseline characteristics			
Age, yrs	64 ± 10	66 ± 11	<0.01
Sex			0.06
Male	761 (79)	170 (73)	–
Female	207 (21)	63 (27)	–
Time since event, days	36 ± 21	42 ± 20	<0.0001
Weight, kg	85 ± 17	82 ± 17	<0.01
BMI, kg/m^2	29.1 ± 5.1	27.9 ± 5.0	0.001
VO$_{2peak}$, ml O$_2$/kg/min	19.5 ± 6.5	18.0 ± 6.1	0.001
Peak RER, V$_{CO2}$/V$_{O2}$	1.09 ± 0.12	1.05 ± 0.11	<0.0001
Handgrip strength, kg	36 ± 11	33 ± 11	0.001
MOS SF-36 Physical Function subscale score	65 ± 26	59 ± 25	0.003
Geriatric depression score[*]	2.8 ± 2.8	3.4 ± 2.8	<0.01
Total cholesterol, mg/dl	161 ± 38	181 ± 42	<0.0001
LDL cholesterol, mg/dl	91 ± 32	107 ± 35	<0.0001
Index diagnosis			
CABG	392 (41)	122 (52)	0.001
Myocardial infarction	312 (32)	64 (28)	0.16
PCI	250 (26)	37 (16)	0.001
Medical therapy/stable angina	13 (1)	10 (4)	<0.01
Exercise-induced changes			
Weight, kg	$-1.1 \pm 3.9^{\dagger}$	$-0.7 \pm 3.3^{\dagger}$	0.16
VO$_{2peak}$, ml O$_2$/kg/min	$+3.2 \pm 3.7^{\dagger}$	$+3.1 \pm 3.7^{\dagger}$	0.73
VO$_{2peak}$, l O$_2$/min	$+0.25 \pm 0.31^{\dagger}$	$+0.24 \pm 0.32^{\dagger}$	0.84
Handgrip strength, kg	$+1.7 \pm 4.5^{\dagger}$	$+1.3 \pm 4.1^{\dagger}$	0.27
MOS SF-36 Physical Function subscale score	$+19 \pm 23^{\dagger}$	$+22 \pm 22^{\dagger}$	0.06
Geriatric depression score[*]	$-1.2 \pm 2.4^{\dagger}$	$-1.5 \pm 2.4^{\dagger}$	0.09

Values are mean ± SD or n (%).

[*] Depression score >5 demonstrates significant symptoms of depression.

[†] Within-group significant difference from baseline at $p < 0.01$.

BMI = body mass index; CABG = coronary artery bypass grafting; LDL = low-density lipoprotein; MOS SF-36 = Medical Outcomes Study 36-item Short Form; PCI = percutaneous coronary intervention; RER = respiratory exchange ratio; VCO2 = carbon dioxide production; V$_{O2}$ = oxygen consumption; V$_{O2}$peak = peak aerobic capacity.