RESEARCH LETTER

ONLINE FIRST

Effects of Statins on Energy and Fatigue With Exertion: Results From a Randomized Controlled Trial

No drug is without adverse effect potential, and fatigue and exertional intolerance are adverse effects reported by patients receiving statins.[1,2] Little direct information is available regarding the typical or average impact of statins on energy or exertional fatigue.

Although many observational reports have cited fatigue and exertional fatigue with statin use, to our knowledge, no randomized trials have addressed this issue to date. Energy and exertional fatigue were measured as tertiary and/or exploratory outcomes in the University of California, San Diego (UCSD) Statin Study, which aimed to examine a range of noncardiac outcomes.[3] We capitalized on these data to evaluate whether moderate-dose statins affected energy and exertional fatigue in a broadly sampled primary prevention population.

Methods. A total of 1016 subjects (692 men 20 years or older and 324 nonprocreative women, with screening low-density lipoprotein cholesterol levels 115-190 mg/dL [to convert to millimoles per liter, multiply by 0.0259] and no cardiovascular disease or diabetes) were randomized equally to 20-mg simvastatin (lipophilic statin), 40-mg pravastatin (hydrophilic statin), or microcrystalline-cellulose placebo, to be taken at bedtime in identical blinding capsules for 6 months.

The off-site study pharmacist matched sequentially numbered bottles to sequential computer-generated randomization assignment stratified by sex (block size, 20; designed by statistician [H.L.W.]). Bottles were transferred to the study site and given to successive eligible subjects by staff blinded to the randomization schedule.[4]

The protocol was approved by the UCSD Human Subjects Protection Program. All subjects (seen exclusively at UCSD) gave written informed consent. The data and safety monitoring board provided independent study oversight.

Outcome. Single-item self-ratings of change from baseline in "energy" and "fatigue with exertion" were used, assessed on 6-month follow-up, and rated (5-point scale) from "much less"(−2) to "much more"(+2) vs baseline.

Energy and fatigue with exertion were rated at baseline from 0 (none) to 10 (maximum possible). All subjects rated energy; the final 397 subjects (a randomized subset) rated baseline fatigue with exertion (omitted initially to limit subject burden, restored for the final 40% of subjects). Missing values of baseline and change score were imputed using the Stata "impute" command (StataCorp). "EnergyFatigEx" values were generated by summing ratings for the energy and fatigue with exertion measures, aligning signs with lower values worse (ie, recoding such that for both variables lower values signified worse status), for baseline and on-treatment, yielding a single outcome (on-treatment score range, −4 to +4).

Statistical Analysis. We assessed the correlation of EnergyFatigEx with actual exercise (baseline assessment: episodes per week of vigorous exercise >20minutes). The unpaired *t* test was used to examine the difference in mean on-treatment EnergyFatigEx in all subjects and women separately. Ordinal logistic regression with robust ("White") standard errors[5] adjusted for baseline values of the combined variable, addressing baseline disparities and regression to the mean (a source of power-eroding variance). The χ^2 test was used to examine whether statins shifted, relative to placebo, the proportion reporting changes of subjectively large magnitude ("much worse" or "much better" vs placebo on both outcomes; the same principle that guides sign tests). Analyses used Stata statistical software versions 8.0 and 11.0 (StataCorp). A 2-sided α level of .05 designated significance.

Results. For CONSORT (Consolidated Standards for Reporting of Trials) and study baseline characteristics, see eFigure and eTable (http://www.archinternmed.com). Energy and predictors of exertional fatigue were comparable at baseline; however, in the subsample with measured baseline exertional fatigue, pravastatin values differed from other arms and influenced imputed baseline values (**Table**). There was a significant relation be-

Table. Change in Energy and Exertional Fatigue Outcome (EnergyFatigEx) for Placebo vs Statin Groups[a]

	Placebo, Mean (SD)	Statin		Simvastatin		Pravastatin	
		Mean (SD)	*P* Value[b]	Mean (SD)	*P* Value	Mean (SD)	*P* Value[b]
All[c]	−0.06 (0.71)	−0.21 (0.87)	.005	−0.25 (0.87)	.002	−0.17 (0.86)	.06
Women	−0.08 (0.72)	−0.39 (1.14)	.01	−0.47 (1.20)	.004	−0.31 (1.08)	.07

[a] EnergyFatigEx score range, −4 to +4. A 0.4-drop (observed for women receiving simvastatin vs placebo) would arise if 4 in 10 treated women cited worsening in either energy or exertional fatigue; 2 in 10 cited worsening on both measures or rated themselves "much worse" on 1 measure; 1 in 10 rated themselves "much worse" on both measures; or combinations of these conditions, with the fractions of subjects for which each statement holds, summing to 1.
Sample sizes: placebo (n = 342), statin (n = 670), simvastatin (n = 332), and pravastatin (n = 338). Sample sizes for women: placebo (n = 110), statin (n = 213), simvastatin (n = 105), pravastatin (n = 108). Mean (SD) baseline EnergyFatigEx values (imputing missing values) (scale, 0 to 20): placebo, 16.8 (2.9); statin, 16.3 (3.0); pravastatin, 16.2 (3.2); simvastatin, 16.5 (2.8). Pravastatin differed significantly from placebo (*P* = .007) and nonsignificantly from simvastatin (*P* = .09).
[b] *P* values are for *t* test of difference in mean for designated statin vs placebo.
[c] Results of ordinal logistic regression, with robust standard errors, adjusted for baseline EnergyFatigEx: statin, β (SE), −0.51 (0.13) (*P* < .001); simvastatin, β (SE), −0.68 (0.15) (*P* < .001); and pravastatin, β (SE), −0.33 (0.15) (*P* = .03).

tween measured baseline EnergyFatigEx and actual exercise (r=0.20; $P<.001$). The drop in low-density lipoprotein cholesterol level with 20-mg simvastatin (49 mg/dL) exceeded that with 40-mg pravastatin (40 mg/dL) ($P<.001$).

Results of t tests of difference in mean on-treatment change in EnergyFatigEx were significant for combined statins vs placebo. Each statin contributed (effects separately significant for simvastatin) (Table). Women were disproportionately affected. The 0.4 mean difference observed for women receiving simvastatin vs placebo would arise if 4 in 10 treated women cited worsening in either energy or exertional fatigue; 2 in 10 characterized both as "worse" or either as "much worse"; 1 in 10 characterized both components as "much worse"; or combinations of these conditions, with the fractions of subjects for which each statement holds, summing to 1. Adjusted for baseline EnergyFatigEx (via ordinal logit), effects on EnergyFatigEx were significantly unfavorable for combined statins and each statin separately.

The balance of those reporting maximal worsening vs maximal improvement ("much worse" vs baseline on each component vs "much better" on each) was adversely shifted for statins vs placebo (P = .002) and for each statin separately (simvastatin, P = .03; pravastatin, P = .01). These are based on small numbers, and findings are provisional.

Comment. To our knowledge, this is the first randomized evidence affirming unfavorable statin effects on energy and exertional fatigue. Effects were seen in a generally healthy sample given modest statin doses, and both simvastatin and pravastatin contributed to the significant adverse effect of statins on energy and fatigue with exertion. Particularly for women, these unfavorable effects were not uncommon. Findings support case reports citing adverse effects to these outcomes and are buttressed by literature rationale.[1,6] These findings are important, given the central relevance of energy and functional status to well-being.

These effects, germane to quality of life, merit consideration when prescribing or contemplating use of statins, particularly in groups without expected net morbidity/mortality benefit, extending to "high-risk" primary prevention and women and elderly persons (including those with coronary artery disease).[7-9] There was a significant relation between EnergyFatigEx and actual activity: reduced activity and exertional tolerance (irrespective of activity) in turn predict hard adverse outcomes. Effects may take time to manifest, as may benefits of statin use. Thus, long-term trials are important, if statin use is to be recommended in younger individuals. Meanwhile, physicians should be alert to patients' reports of exertional fatigue or diminished energy during statin use.

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