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The UCSD Statin Study: a randomized controlled trial assessing the impact of statins on selected noncardiac outcomes

Beatrice A. Golomb[a,b,c,*], **Michael H. Criqui**[a,b], **Halbert L. White**[d], and **Joel E. Dimsdale**[e]

[a]Department of Medicine, University of California, CA, USA

[b]Department of Family and Preventive Medicine, University of California, CA, USA

[c]Department of Psychology, University of California, CA, USA

[d]Department of Economics, University of California, CA, USA

[e]Department of Psychiatry, University of California, CA, USA

Abstract

There has been persistent controversy regarding possible favorable or adverse effects of statins or of cholesterol reduction on cognition, mood and behavior (including aggressive or violent behavior), muscle function, and quality of life. The UCSD Statin Study seeks to ascertain the beneficial or adverse effects of statin cholesterol-lowering drugs on a set of noncardiac endpoints, including cognition, behavior, and serotonin biochemistry. The study will enroll 1000 subjects (minimum 20% female) of mixed ethnicity from San Diego. Subjects must be age 20 and older, postmenopausal if female, without known cardiovascular disease or diabetes, and with LDL-cholesterol between 115 and 190 mg/dl. Subjects will be randomized to a double-blind, placebo-controlled trial with assignment 1/3, 1/3, 1/3 to placebo, simvastatin 20 mg, or pravastatin 40 mg (equipotent LDL-cholesterol-lowering doses for drug arms with simvastatin and pravastatin chosen to represent the extremes of the lipophilicity spectrum) for 6 months of treatment followed by 2 months postcessation follow-up. Primary outcomes are cognition (cognitive battery), irritability/aggression (behavior measure), and serotonin (gauged by whole blood serotonin), assessed as the difference between baseline and 6 months, judging combined statin groups vs. placebo. Secondary outcomes include mood (CES-D and Wakefield depression inventory), quality of life (SF-12V), sleep (Leeds sleep scale, modified), and secondary aggression measures (Conflict Tactics Scale; Overt Aggression Scale, Modified). Cardiovascular reactivity will be examined in a 10% subset. As additional secondary endpoints, primary and selected secondary outcomes will be assessed by statin assignment (lipophilic simvastatin vs. hydrophilic pravastatin). “Reversibility” of changes, if any, at 2 months postcessation will be determined. If effects (favorable or unfavorable) are identified, we will seek to ascertain whether there are baseline variables that predict who will be most susceptible to these favorable or adverse noncardiac effects (i.e., effect modification).

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*Corresponding author. Department of Medicine 0995, University of California, San Diego School of Medicine, 9500 Gilman Drive, La Jolla, CA 92093-0995, USA. Tel.: +1-858-558-4950x201; fax: +1-858-558-4960. bgolomb@ucsd.edu (B.A. Golomb).

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Keywords

HMG-CoA reductase inhibitors; Statins; Serotonin; Risk–benefit; Cognition; Aggression

1. Background

Statins are important and widely prescribed drugs, with well-documented and incontrovertible cardiac benefits. However, controversy remains regarding the existence and impact of noncardiac effects, including central nervous system (CNS) effects. The University of California-San Diego (UCSD) Statin Study, a National Institutes of Health/National Heart Lung and Blood Institute-funded double-blind, placebo-controlled study, seeks to address these issues through a complex battery of tests assessing noncardiac outcomes pertaining to cognition, behavior, quality of life, and biochemistry, among other endpoints. This paper provides the general methodology employed and addresses certain theoretical issues in study design.

Statin cholesterol-lowering drugs (HMG-CoA reductase inhibitors) are the most prescribed drugs in the United States and the world and contributed substantially to prescription drug cost increases in 2001 [1–3]. With tens of millions of U.S. users projected to follow Adult Treatment Panel III cholesterol guideline revisions, the need to understand their full range of effects becomes increasingly important [4,5]. Most randomized controlled trials (RCTs) examining effects of statins have focused on cardiovascular benefits of these drugs, which are substantial and incontestable. These benefits are sufficient to produce clear overall mortality benefit, on average, in defined subgroups [e.g., middle-aged men with coronary artery disease (CAD), or at high CAD risk] [6]. However, net mortality benefit has not been demonstrated, nor even a trend suggested, in studies focusing on non-high-risk populations [7,8]. Nor have women, even at high CAD risk, evidenced any trend toward net mortality benefit with statins. Even in the study showing the largest mortality benefit in men, a nonsignificant 12% increase in odds of mortality was seen in women—though the number randomized was small and confidence intervals were wide [6]. The net impact in older elderly persons (i.e., age over 75 years) has not been defined; observational evidence suggests that effects may be less favorable or frankly unfavorable, and the recent Prosper Study, in subjects age ≥70, found less than expected cardiovascular disease benefit, and no trend toward mortality benefit, despite selection of elderly at specially high cardiovascular risk [9,10]. Newer guidelines, and exhortations to treat persons “missed” by guidelines, may increasingly result in treatment of those for whom a favorable mortality risk–benefit ratio has not been clearly shown [11]. For this reason, it becomes increasingly vital to understand the impact of statin drugs on noncardiac morbidity (favorable and adverse), so that noncardiac effects can be considered together with cardiac benefits, to provide a sound risk–benefit basis for treatment decisions.

The UCSD Statin Study seeks to clarify noncardiac effects of statins, particularly CNS effects. The effects of low or lowered cholesterol on cognitive function, on aggression, and on serotonin biochemistry remain controversial, and only limited data are available. This study seeks to begin to remedy this gap. The conceptual issues that inform the methodology

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are reviewed in detail in a companion paper [12]. The present report describes the methods of the UCSD Statin Study.

2. Trial design and methods

2.1. Overview

The study is a double-blind, randomized, placebo-controlled trial of 1000 subjects, treated for 6 months with equal likelihood of receiving simvastatin 20 mg, pravastatin 40 mg, or placebo. A 2-month postcessation follow-up will evaluate whether treatment effects on tested outcomes reverse or whether rebound effects occur on cessation. Literature reviews have supported important rebound effects with alterations of biochemistry for a host of pharmaceutical agents, and some evidence has suggested possible rebound worsening in cardiac outcomes on statin discontinuation, although this was in the setting of acute coronary syndromes [13,14]. Additionally, we will assess whether rebound increases in cholesterol occur following statin discontinuation: statins lead to reduction in coenzyme Q10 and isoprenoids; and coenzyme Q10 reportedly exerts feedback inhibition on HMG-CoA reductase, while isoprene intermediates exert feedback inhibition on mevalonate kinase [15,16]. Thus, there is a theoretical possibility that a rebound increase in cholesterol production could ensue following statin discontinuation, resulting from (for instance) relative coenzyme Q10 depletion.

2.2. Inclusion and exclusion criteria

Subjects are eligible if they are male over age 20 or female and postmenopausal (or unable to bear children); have low density lipoprotein (LDL)-cholesterol between 115 and 190 mg/dl; do not have known cardiovascular disease or diabetes; do not have active liver disease or transaminase levels exceeding two times the upper limit of normal or severe renal disease; and are not on drugs anticipated to have drug interactions (e.g., azole antifungal drugs, selected antibiotics such as erythromycin, or nefazodone).

Persons with cardiovascular disease or diabetes mellitus were excluded because high cardiovascular risk individuals have greater absolute benefit from statin therapy, and the risk–benefit ratio, on average, is clearly favorable (at least for middle-aged or moderately elderly men) as gauged by overall mortality effects; the appropriateness of randomizing such individuals to placebo would be in question. A similar rationale guided exclusion of those with LDL-cholesterol exceeding 190 mg/dl. Those with LDL-cholesterol under 115 mg/dl were deemed less likely to receive lipid lowering treatment in practice, and findings in these individuals might be presumed to not generalize to those at risk of receiving statin treatment. Since the trial was funded, some studies such as the Heart Protection Study and the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study have shown cardiovascular benefits with statins irrespective of pretreatment LDL, with doses as high as 80 mg of atorvastatin—equivalent to eight times the lipid lowering drug dose used here—in high risk persons [17,18]. Thus, if effects appear predominantly in the lower reaches of cholesterol, lower than typically achieved with the dose and LDL exclusion criteria employed here, this study may not detect such effects. However, the comparatively low doses—by current standards—were selected prior to publication of these recent studies; and

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with the intent to mitigate risk, if any, to study subjects, in light of the noncardiovascular focus of the study. Any medical problem expected to preclude follow-up over an 8-month study was grounds for exclusion. Although mild psychiatric history or problems, or use of psychiatric medications (other than nefazodone, which may interfere with metabolism of simvastatin), were not reasons for exclusion, significant active psychiatric problems or active psychosis constituted an exclusion criterion. For persons with certain other significant psychiatric problems, the study psychiatrist adjudicated whether admission to the study was appropriate.

2.3. Gender

Our study relatively emphasizes men because violence, coronary artery disease, and statin treatment are more prevalent in men than in women; women are at lesser risk of heart disease; for a given level of risk, the evidence for treatment with statins is less persuasive for women; women are at lower baseline risk of violence; and no study has shown an effect of low or lower cholesterol on violence in women. Thus, the power to detect a given effect size for violence may be enhanced by relative emphasis on men. Four factors influenced the gender-ratio for this trial:

1. Violence: Violent crime by men was nine times as common as in women in a prospective cohort analysis linking low cholesterol to arrests for violent crimes [19]. The link between low cholesterol and violent death was also lower in women than men, not just for absolute but also for relative risk, in a study capitalizing on this population, and the link did not approach significance in women [20].
2. Benefit of cholesterol reduction: Women have lower cardiovascular risk than men; receive cholesterol treatment less commonly than men; and while cardiac benefits with statins in high risk women are well established, no published trial has shown overall mortality benefit in women, even those at high cardiovascular risk, providing less foundation for dictating treatment [6,21].
3. Teratogenicity: Women who remain fertile are poor candidates for statins, which are teratogens. Therefore, lipid reduction and statin treatment are less commonly undertaken in women.
4. Cognition: Women may, however, be similarly subject to cognitive effects and therefore should not be excluded [22,23]. Moreover, women are increasingly recipients of treatment. They have lower weight on average and have been reported to experience more adverse effects and less favorable outcomes from many drugs and interventions, including those directed to cardiovascular disease [24–29]. Therefore, reasonable representation of women is sought in order to evaluate whether differences by gender are suggested. For this reason, we plan to include a minimum of 20% women (n=200) in this study, with more than 20% anticipated to be enrolled.

If effects on studied outcomes are detected, and if trends suggest possible differences in women, a larger study with strong female representation may be conducted.

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2.4. Age

No older age limit was employed because information on older elderly is important and older elderly are often excluded from study. The risk–benefit ratio for cholesterol reduction at any cardiovascular risk level for older elderly remains unclear. No randomized trials have evaluated the impact of statins on overall mortality in high-risk older elderly. Some additional issues are as follows.

1. Higher cardiovascular risk: Older elderly have been interpreted by some to have greater expected benefit from cholesterol reduction due to their higher cardiovascular risk: higher baseline risk would imply greater absolute risk reduction if relative risk reduction could be presumed comparable [30]. This would lead to more favorable risk benefit profiles, provided that risks of harm were unchanged. However:
2. Attenuated relationship of lipids to mortality: The relation of lipids to mortality flattens and then strongly reverses with increasing age from elderly to older elderly [9]. It is possible that this relationship is mediated by confounding, with illness causing low cholesterol in some; however, it is also possible that causal factors contribute or predominate.
3. Higher risk of adverse effects: Elderly, and particularly older elderly, are more vulnerable to drug adverse effects [31].
4. Effects, if any, on cognition, mood, or muscle function may be particularly critical in the older elderly. Changes in cognition, depression, and fitness have marked mortality implications in this group [22,32–45].

Older elderly may be less likely to seek participation in RCTs because of health, transportation, cognitive, or other problems. Screened older elderly may have low rates of admittance into randomized trials, even trials for which older elderly are eligible or sought, and may have high dropout rates once enrolled [46,47]. These factors contribute to the low likelihood that this study will be separately powered to evaluate the impact of statin treatment on older elderly. However, if suggestive trends are seen, they may define a need for additional study focusing on this group. Moreover, if older elderly are included in several studies, and if common outcomes are measured, meta-analysis may help to define differences, if any, in outcomes in this group.

3. Main outcomes

3.1. Cognitive tests

Digit Vigilance, Recurrent Words (% hits), Elithorn Maze completion time, and Grooved Pegboard insertion time will be performed [48–51]. Such tests, characterized as tests of attention (former two) and psychomotor speed, showed impairment in previous smaller studies examining effects of statins and constitute, together, the primary outcome [22,23,52]. Few tests isolate single neurally defined brain functions. Tests of selected other functions showed a trend toward impairment, and additional cognitive measures will be assessed as secondary endpoints.

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Of note, since this study was funded, findings of the large randomized Heart Protection Study (HPS) have been published (*n*=20536), in which cognition was assessed in association with simvastatin use, employing the Telephone Interview for Cognitive Status [53]. No effect on cognition was observed. Despite the large sample, however, several factors limit the generalizability of these findings:

1. A cognitive measure that targets domains different from those affected would not be expected to capture the effect, even with a large sample. The measure used in HPS is not designed to tap psychomotor speed and visual attention, the domains in which impaired cognition have been reported; whereas such measures constitute our primary endpoints.
2. An active run-in excluded persons with early problems on statins, thus potentially excluding those who experienced cognitive effects.
3. The study focused on persons with high risk of cerebrovascular disease (persons with known vascular disease or diabetes), in whom benefits to cognition from reduced stroke risk might be expected to counterbalance deficits to cognition from other mechanisms.

Indeed, it is striking that no trend toward cognitive benefit with statin treatment was seen despite a marked reduction in stroke incidence in this population at high stroke risk, potentially consistent with a counterbalancing negative influence of statins on cognition. Thus, there remains a need to reappraise cognition using properly selected tests, without an active run-in, and in a group less selected for risk of stroke, conditions that are met in the present study.

3.2. Point subtraction aggression paradigm (PSAP)

The first session of the PSAP represents a primary outcome [54–57]. This comprises a 25-min test in which subjects sit before a computer screen with a bar with two response options. They may press button “A” 100 times to produce one point worth 10 cents. They may press button “B” (“aggressive” option) 10 times to produce a 10-point subtraction from a fictional opponent or “partner” with no point advantage to themselves. Points are subtracted from the subject’s point-accumulation counter randomly, every 6 to 120 s (potentially “provoking” the subject); the subject is led to believe these subtractions originated with the fictional partner [55]. Current points earned are displayed in the center of the computer screen.

The PSAP has been shown to relate to serotonin state the hypothesized mediating factor between cholesterol and violence and to aggression/violence [56–58]. An increase in aggressive responding by PSAP occurred in healthy males with a serotonin-lowering drink [59,60]. In personality-disordered men, performance on the PSAP correlated inversely with a proxy measure for central serotonin and correlated positively with one aggression scale (Brown Goodwin), though not another (Buss Durkee Hostility Inventory Assault scale) [57]. The PSAP also correlates with actual violence; violent parolees score significantly higher than nonviolent parolees [58]. Because the standard PSAP is very time- and labor-intensive to perform, an abbreviated version will be used consisting of the first run of the series of PSAP trials. We have separately validated use of this procedure.

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Despite the advantages of this instrument, limitations in use of the PSAP in this population have been identified, including repetitive motion problems and discomfort in some older subjects. As noted below, secondary measures of irritability are also used.

3.3. Serotonin biochemistry

Whole blood serotonin is the only peripheral serotonin measure demonstrated to correlate with aggression in an unselected epidemiologic cohort (as well as in some specialized populations, though not others) [61–63]. Both this property and its relative stability led to its selection as the primary outcome measure of serotonin for the present study. Again, low measures of central serotonin (5-HIAA and hormonal indices) but high measures of whole blood serotonin are linked to aggression. The inverse relation between central and blood serotonin is consistent in other settings; and treatment with selective serotonin reuptake inhibitors (SSRIs), which raises central serotonin, is linked to reductions in whole blood serotonin [64,65].

Though a larger literature relates cerebrospinal fluid (CSF) 5-HIAA to violence, lumbar puncture is more invasive and less tolerated by subjects. Prolactin response to fenfluramine challenge, a previously popular measure of central serotonin function shown to relate to aggression, is no longer tenable due to adverse effects of fenfluramine leading to its withdrawal from the market [57,66–75]. Use of a blood measure that has been related to CSF 5-HIAA—with inclusion of two secondary measures of serotonin function from blood and urine (below) that have been related to aggression—will reduce the likelihood that an important effect on serotonin will be missed and increase the likelihood that a serotonin measure will be identified that is linked both to cholesterol reduction and to aggression, which could potentially be followed in future studies of at-risk subjects on lipid-lowering drugs.

4. Secondary outcomes

4.1. Cardiovascular reactivity test

For a stratified random subset of 100 subjects, cardiovascular reactivity testing will be performed at baseline and following 6 months of treatment. Blood pressure and heart-rate monitoring equipment will record changes in blood pressure and heart rate, in subjects who agree to participate in a validated cardiovascular reactivity paradigm, entailing a speaking stressor. This is a standardized paradigm developed and widely used at UCSD and approved by the UCSD Institutional Review Board [76–83]. Subjects are given instructions for a speaking task after being seated for 15 min (a departure from the 30 min generally used). The speech stressor consists of a 3-min preparation phase and a 3-min speaking phase. The two speaking scenarios used (one at baseline and one at 6 months) have been shown to produce comparable effects on cardiovascular reactivity testing [79]. One asks subjects to defend themselves from a charge of shoplifting, and the other to argue with an auto sale and repair facility that is failing to honor a warrantee.

Catecholamines will be measured in this subset, prior to cardiovascular reactivity testing. Although catecholamine reactivity testing would be desirable, subject blood draw burdens

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(testing requires placement of an indwelling catheter) and substantial laboratory burdens for these particular tests precluded inclusion of such measures [84–86].

This testing will evaluate whether reactivity profiles may predict aggressive tendencies or response (beneficial or deleterious) of mood and personality to statin drugs. There is an existing literature in which it is supposed that both low and high cardiovascular reactivity may be linked to violence; high reactivity may relate to reactive, emotionally induced violence, while low reactivity may relate to psychopathic, conscienceless violence [87–90].

4.2. Cognitive function: mental flexibility, memory, and combination

In addition to primary cognitive measures, brief testing of mental flexibility and memory will also be done, including the Stroop Interference Test for mental flexibility (and psychomotor speed), Digit Symbol (memory), and Digit Span (immediate memory), Trail Making, and Hopkins Verbal Learning [91,92]. The American National Adult Reading Test (ANART) will be used as it is a test considered relatively insensitive to change that is strongly correlated with overall cognitive function. Table 1 shows the nonlaboratory measures and their timing.

4.3. Measures related to aggression, personality, and risk of injury

Additional secondary measures of aggression will be performed as endpoints and at baseline to assess whether existing aggression, harm avoidance, or conscientiousness measures predict which individuals (if any) are susceptible to adverse effects of statins and whether lipid modification with statins cause changes in these measures. The Conflict Tactics Scale (Part II for all; Part I for subset), Overt Aggression Scale-Modified (OAS-M), and a Statin Study Questionnaire (SSQ)-Conflict subscale will be assessed for predictive power and susceptibility to change; and the Life History of Aggression for predictive relevance only will be administered to judge aggressive responding over a range of timescales [93–98]. Additional measures, directed to behaviors of clear clinical relevance, include an instrument focusing on phone and driving behaviors (SSQ-Conflict) and a small set of question asked of spouses (or designated others) at 3 months, inquiring whether a change has been noted (increase or decrease) in irritability.

4.4. Mood, personality, sleep, and quality of life measures

Depression will be measured using the Center for Epidemiological Studies-Depression Scale (CES-D), an inventory shown to be valid and responsive to differences in physiological parameters [99]. The evidence of a relation of cholesterol to depression in published studies has been mixed and appears to be substantially less consistent than the relation of cholesterol to behavior, including suicide [23,100,101]. Nonetheless, it will be important to assess the effect of substantial reductions in cholesterol, such as those produced by simvastatin and pravastatin, on measures of depression. Sleep quality will be measured with a modification of the Leeds Sleep Questionnaire, according to which subjects on lovastatin found it “more difficult to get to sleep” than those on pravastatin [102]. A sleep laboratory study found markedly increased wake time after sleep onset and increased stage 1 sleep in lovastatin but not pravastatin compared to placebo [103]. We will also assess subjective sleep quality and quality of life using the 12-item Short Form Health (SF-12v2). There may

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be instances (in addition to some of the above) in which cholesterol reduction leads to benefit to mood or personality; such benefits, as well as risks, should be assessed.

4.5. Secondary serotonin measures

Urinary 5-HIAA, found to be low in delinquent adolescent males, constitutes one secondary serotonin measure [104].

Serum tryptophan, the precursor to central serotonin, will also be measured. A mechanism by which low cholesterol may produce low serotonin has been detailed elsewhere [105]. Because of cost considerations, tryptophan testing will only be performed in a subset.

4.6. Laboratory testing

Testing will be performed at baseline (twice for lipids only), 1 month (early treatment), 6 months (end of treatment), and 8 months (posttreatment follow-up). Lipids (high-density lipoprotein), total cholesterol, LDL-cholesterol, and triglycerides will be obtained, fasting on and off treatment (at baseline and 6 months), and 2 h after a high glucose load, on and off treatment (at the 1- and 8-month visits). Creatine phosphokinase will be obtained at any time subjects report unexplained muscle symptoms. The 10% subset assigned to cardiovascular reactivity testing will undergo catecholamine testing at baseline and at 6 months of treatment. Table 2 shows the laboratory testing schedule.

4.6.1. Stored samples—Additional blood will be drawn for archiving at baseline and 6 months, and frozen at −70 °C, in the event that subsequent evidence suggests the value of additional tests as risk predictors.

4.7. Analysis, sample size, and power

4.7.1. Primary analysis—The primary analysis for this RCT is a *t*-test for difference in means (or mean change in scores following 6 months of treatment) for each of the three primary outcome measures to assess whether assignment to cholesterol lowering treatment led to change in behavior, cognition, or biochemical measures. Data will be cleaned, and observations with missing variables will be dropped (if missing dependent or main independent variable) or imputed. Univariate analysis will be performed and treatment and control groups will be compared on baseline characteristics to assess success of randomization, thus assuring appropriateness of findings from this main analysis.

4.7.2. Secondary analyses

1. Analogous to the main analysis, *t*-tests for difference in means will be performed to assess whether the change from baseline to posttreatment differs for the treatment vs. control group for secondary measures, including ancillary questionnaire and biochemical measures.
2. Testing will determine whether response differs in males and females; if significant effect modification is found, results will be stratified by sex.
3. To assess whether treatment (the main independent variable) interacts with baseline characteristics to determine changes in outcome variables—to assess, for instance,

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whether there is a susceptible or protected subset—univariate and bivariate analyses will be performed to inform variable transformation and prospective interaction terms for multiple regression. Models may include age and sex (limited adjustment model); alcohol, smoking, education, ethnicity, prior history of violence, prior history of depression, and prior accident history (psychosocial model); alcohol, smoking, serotonin, copper, zinc, lead, gamma amino butyric acid (GABA), plasma catechols, reactivity, testosterone, baseline lipids, antihypertensive treatment and estrogen (biochemical model); or all these factors (full model). Interaction terms will be tested based on theoretical and empirical considerations. Standard regression diagnostics including residual analysis will be performed.

4. Analysis will also be performed of the joint effect of baseline cholesterol level and cholesterol change on response to challenge tests, cognition, and biochemical factors (as well as on secondary measures) adjusting for key covariates to ascertain if a "dose-response" effect is supported.

4.7.3. Cross-sectional evaluation—In addition to assessing the impact of cholesterol treatment on behavior, cognition, and biochemistry, regression analysis on the whole enrolled population at baseline (including those assigned to treatment and control) will provide important cross-sectional information of the relationship of psychosocial and biochemical factors to behavior, cognition, and biochemistry, as well as to mood. The size of the database will permit replication and extension of previous findings on biochemical effects of factors like copper and zinc on behavioral outcomes and of use of antihypertensives, including calcium channel blockers, on these outcomes [106,107]. Regression analysis will permit the magnitude of the effect on the primary outcomes from lipid lowering treatment to be put into context, by comparing the magnitude of impact of statin treatment, if any, to the magnitude of the relationship of known predictors, like age, gender, alcohol consumption, smoking, and baseline biochemistry.

4.7.4. Adjustment for multiple comparisons—We specify three main hypotheses pertaining to (1) cognitive outcomes, (2) aggression/irritability, and (3) biochemical measures. In (1) and (3), there are implicit subhypotheses, i.e., there are four measures of cognitive outcome that together comprise the primary cognitive outcome. The primary test will compare placebo to the cholesterol lowering arms combined. A secondary test will compare simvastatin to pravastatin. Each of these two tests will be performed at the 0.05 level.

Obviously, special steps are needed to maintain a correct experimentwise alpha level with multiple outcome measures. Crude adjustments using Bonferroni's inequality for multiple measures are probably overly conservative because an individual who has a marked response on one measure will also respond on the others (thus contradicting the assumed independence of tests on which Bonferronization is based). In addition, relatively more alpha should be "spent" on the hypothesis which entails more tests. Fortunately, in a randomized experiment like the present one, it is possible to obtain an exact, nominally correct alpha level by referring any test statistic to its permutation distribution under the

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randomization scheme (see Efron and Tibshirani [108] for a review of permutation testing). There remains the issue of determining a reasonable test statistic. We will use the smallest nominal *p*-value obtained by performing a Bonferronized test of each of the three main hypotheses as the test statistic. Use of this test statistic results in an equal division of the available alpha across our three main hypotheses. (Further Bonferronization for the three main hypotheses turns out to be irrelevant since the alpha level reported by permutation procedure is invariant with respect to monotone transformation of the test statistic.) Analogous analysis will be performed using refinements of the Bonferroni method such as that of Hochberg [109].

One-tenth of subjects, for a total of 100, will undergo cardiovascular reactivity testing. The permuted blocks design will result in a tenth of the subjects in each block being assigned to stress testing. Each block will consist of equal numbers of subjects in the following categories: stress test and placebo, stress test and pravastatin, and stress test and simvastatin. In effect, there are two randomizations: one to medication arm and one to stress test or not. The permutation tests, to determine whether treatment arm affects behavioral/biochemical reactivity outcomes, will be constructed by performing permutations with respect to the second randomization only.

4.7.5. Effect size considerations—The planned study size is 1000 patients—333 patients in each of the three arms of which 100 (33 in each group) will be stress tested. We consider the power of the principal tests (described in Adjustment for multiple comparisons). Some assumption regarding the correlation of the dependent measures is required, but we have no data on which to estimate those correlations. A conservative procedure (i.e., one which understates the power) is to assume that the tests are uncorrelated. Given this and well-known asymptotics concerning permutation tests (see Rao [110]), the distribution of the attained *p*-value for the permutation test described under Adjustment for multiple comparisons is that of the smallest of p_i/k_i, i=1,…,14, where p_i is the attained *p*-value for the unpaired *t*-test comparing placebo to both cholesterol lowering arms combined on the *i*th outcome measure, and k_i is an adjustment factor equal to 12 for the cognitive measures, 21 for the biochemical measures, and 9 for the stress tests [110].

Table 3 presents the effect size for which the test procedure has power 0.9. There is one column pertaining to the comparison of placebo to active medication and another column pertaining to comparison of simvastatin to pravastatin. Calculations are based on 600 patients because of hypotheses that some effects may occur only in males or with lipophilic agents (the 800 males include 267 placebo and 267 lipophilic assignees, providing a total of 533, approximating the sample size of 600 for which effect size calculations were performed).

1. Several of these calculations are based on data which involved multiple measurements. Selection of those measures for which an effect was seen, in guiding our sample size calculations, may favor portrayal of spuriously strong correlations in small samples. For the cognitive tests previously tested and included in our own proposal, all tests showed a trend toward worsening in the treatment group. Our effect sizes are calculated for those tests that were shown to be

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significantly affected in the prior study. An adequate effect size should be seen on other important tests of memory and mental flexibility with the larger sample size.

2. Effect size calculations take inadequate account of the added variability (and resulting reduced ability to detect an effect) enforced by: inclusion of women, for whom effects on violence (but not cognition) are believed to be much smaller; inclusion of subjects on SSRIs in whom an effect may not (or may) be seen; failure to exclude some individuals at heightened risk of dropout from the study, which may reduce study power; and inclusion of two drug arms (as well as a placebo arm), which requires that samples be large enough for the arms to be compared. Thus, there are scenarios in which only a larger "true" effect size would be discernible, providing for need for the large sample.

4.7.6. Intention to treat analysis—The primary analysis will be performed on an intention to treat basis. An "on-treatment" analysis will be conducted for comparison. Regarding on-treatment analyses, compliance monitoring in active treatment vs. placebo group will help to distinguish effects of compliance specific to the drug vs. those related, presumably, to the individual.

5. Randomization and blinding

Consecutive subjects will be assigned randomly to placebo, simvastatin, or pravastatin in equal numbers. Subjects will be selected to undergo behavioral challenge testing using a permuted blocks design with a modest block size. Blinding will be accomplished by use of active and placebo medication in identically appearing forms and packaging distinguished only by code number. Materials needed to break the code will be available in the pharmacy, and the data manager will retain a set of sealed codes in an office space remote from the study site and main database. All subjects, but no investigators, will be unblinded to assignment following each subject's completion of study participation.

6. Treatment monitoring and safety

Liver function test monitoring will be performed both prior to and during testing; subjects will be excluded if baseline transaminase values exceed twice the upper limit of normal and will be discontinued from participation if transaminase values exceed three times the upper limit of normal. Subjects reporting muscle problems will receive creatine phosphokinase (CPK) monitoring, although termination of participation will not rest exclusively on the finding of elevated CPK due to findings suggesting that statins may induce non-CPK-elevating myopathy [111]. A 24-h hotline will be available for subjects with questions or concerns outside clinic hours; subjects will be encouraged to page the number if they have possible adverse events of any type that lead to concern. An experienced psychiatrist will be available for assessment of any subject reporting possible psychiatric problems; the psychiatrist will adjudicate whether continued participation in the study is acceptable, in the face of possible mood or psychiatric changes. The psychiatrist will also provide counsel in instances in which psychiatric concerns lead to questions regarding eligibility for participation. Subjects in any group reporting possible adverse effects that they attribute to participation may discontinue at any time, and termination for cause will be considered an

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endpoint. Those willing to continue participation will receive the 2-month posttreatment cessation follow-up. Since a major focus of the study is evaluation of noncardiac effects, the primary comparison will be based on the terminal on-treatment visit (whether at 6 months or earlier) to preclude exclusion of the very subjects who may contribute most to the assessment. Comparison of termination for perceived adverse events will be performed by study assignment as a secondary endpoint.

7. Follow-up

Assessments of primary and secondary outcomes, compliance, and assessment for new events will be performed at 1, 6, and 8 months (2 months after treatment discontinuation). Cardiovascular reactivity in the 10% random subset will be retested only at 6 months. A limited 3-month visit focusing on compliance and eligibility (adverse effect monitoring, cardiovascular status) will be conducted. New coronary artery disease may require that patient to be dropped from the study, as treatment to lower cholesterol may then be mandated. The posttreatment measure will allow assessment of whether changes in primary or secondary endpoints (if any) are fully reversed on discontinuation, or if “rebound” effects on examined outcomes occur, irrespective of whether changes with treatment are observed. Recent evidence has been taken to suggest that those who discontinue statin treatment may experience increased cardiovascular events relative to those who continue treatment, and perhaps relative to those never treated, though alternative explanations for these findings are possible [14]. These findings relate to settings of acute cardiac disease and are relevant to the current study primarily as reminders that rebound effects of drug discontinuation can occur and should be sought.

7.1. Assessment of medication adherence

Electronic monitoring of adherence (“electronic event monitoring” or EEM) via Medication Event Monitoring System (MEMS) TrackCaps (Aprex) will be used on all subjects. Microprocessor chips in the cap of the pill container record the date and time of each presumptive dose. Adherence measures using self-report (SR) and pill counts (PC) systematically overestimate compliance: setting an 80% criterion for good adherence, 95% of subjects were adherent by SR, 91% by PC, and only 76% by EEM [112]. Among subjects of whom all had poor adherence by EEM, 90% were adherent by SR and 67% by PC [112]. Since not all subjects misrepresent compliance similarly, precision in compliance measurement will be reduced, and if misrepresentation is differential, bias may be introduced. For these reasons, EEM is preferred over self-report or pill count.

8. Discussion

This study represents the first large study to systematically evaluate the impact of statins, selected at the extremes of hydrophilicity and lipophilicity, on mood, cognition, serotonin biochemistry, and other biochemical and quality of life relevant outcomes. It will provide information that will determine whether existing concerns are supported or controverted, and whether benefit to cognition or its opposite is noted.

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8.1. Study advantages (with provisos)

1. This study, unlike most prior studies of lipid lowering agents, does not expressly exclude what may be the most susceptible subset: those with a history of psychiatric problems, alcohol use/abuse, and noncompliance. This reduces the likelihood that an effect most evident in this subset will be missed. However, although such subjects will not be actively excluded, self-exclusion from study participation will remain; and the study psychiatrist may make determinations that individual subjects are not suitable for inclusion.

2. Large lipid reductions occur with statins, the class of lipid lowering drug used here, reducing the likelihood of a missed effect, if total cholesterol or LDL-cholesterol are causally related to the outcomes assessed. However, effects could be missed if they occur selectively in persons with high or low cholesterol, who are excluded from participation, or in those treated more aggressively than here. Regarding the first point, if in some persons high cholesterol serves a biological function, e.g., enhanced transport of coenzyme Q10 or fat soluble vitamins to overcome tissue deficiencies or supply increased need, then such persons may be more subject to problems with cholesterol reduction. Regarding the second point, if effects relate selectively to very low or very reduced cholesterol, then persons with low baseline cholesterol—who are excluded from participation, but increasingly receive treatment in the community if at high cardiovascular risk—may be selectively affected, as may persons receiving greater statin doses than given here.

3. Simvastatin and pravastatin are commonly used agents, so the results will have direct clinical relevance.

4. This study will permit a first-pass assessment of whether CNS and biochemical effects of statins differ by lipophilicity. This will either strengthen or negate the rationale for preferential use of certain statins, based on hydrophilicity, to avert adverse effects.

5. The results will be important to clinical practice whether an effect is demonstrated or excluded. Concerns about effects of lipid reduction using statins may be ameliorated if results are negative, at least for low dose usage in patients with similar risk profile. Conversely, if effects are demonstrated, in all or a susceptible subset, physicians will have information permitting more reasoned consideration of (selected) risks as well as benefits in treatment decisions.

6. The study will take steps toward characterizing the time course of the effect (if any) of statin use on cognition, behavior, biochemistry, and reactivity (though effects requiring in excess of 6 months to develop will not be identified) and will assess the reversibility of effects (if any are seen) with drug discontinuation (within a 2-month period).

7. The study incorporates, and has as a main outcome measure, assessment of a possible biochemical mediator for behavioral/mood effects, namely, low serotonin. Serotonin assessment may enhance understanding of the mechanism and time course of effect, if any. Secondary outcomes will assess impact of treatment on

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other factors that could influence an effect—favorable or adverse—of treatment on behavior and cognition, such as GABA, corticosteroids, or testosterone, blood pressure, insulin/glucose, and other parameters. Blood will be archived for possible future testing, e.g., of coenzyme Q10, for correlation with noncardiac adverse outcomes, if any [113,114].

8. This study will add information on a measure of behavioral susceptibility short of violent events.

9. The study may be capitalizing on a critical time window for evaluation of the effects examined here, as statins are increasingly used in lower-risk and lower-cholesterol populations, following findings of (and editorials regarding) The West Of Scotland Coronary Prevention Study and the Cholesterol and Recurrent Events Trial, the Air Force/Texas Coronary Atherosclerosis Prevention Study, and HPS; it may be increasingly difficult in the future to identify an eligible population not already receiving treatment [115].

10. The baseline measurements in this RCT will provide cross-sectional information on the relation of biochemical and sociodemographic factors to questionnaire measures such as conscientiousness, and between some questionnaire measures (e.g., related to mood, conscientiousness, violent tendency, alcohol use).

11. This study will allow assessment of within-individual correlation of changes in one measure across time to changes in other measures.

8.2. Study limitations (with provisos)

1. Effects of statins may not generalize to other lipid lowering treatments. It is possible that other biochemical or fatty-acid-related effects distinct from cholesterol reduction relate to behavior and biochemistry, and that in prior observational and experimental studies in humans and nonhuman primates, low and lowered cholesterol appeared to be connected to biochemistry and behavior only because the methods producing low and lowered cholesterol affected this factor as well. Statins might fail to show such an effect. Specific fats have been shown to affect neurotransmitter factors, cognitive function, and behavior in animal studies [116]. Conversely, it is possible that if effects on cognition, behavior, and/or biochemistry are seen with one or both statins, they could represent drug or class-specific effects that do not generalize to other methods of cholesterol reduction. The relation between LDL-cholesterol metabolism in the plasma to that in the brain remains unestablished; however, cholesterol concentration in the cell membrane is highly influenced by cholesterol concentration in the surrounding environment, so that agents affecting cholesterol production in the brain could provoke different brain effects than agents that do not. Since statins dominate in clinical use among available lipid lowering drugs, evidence that statins do not (or do) produce adverse (or positive) effects on reactivity, on cognition, and on biochemistry will be vitally important irrespective of whether and how they affect brain cholesterol.

2. The decision to use statins at the extremes of the hydrophilicity/lipophilicity spectrum (pravastatin and simvastatin) maximizes the ability to exclude an effect of

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lipophilicity if none is present. Peripheral actions can have secondary central consequences, and CNS effects need not imply central penetration of the drug. This choice also offers the best opportunity to demonstrate an impact of lipophilicity if one is present. However, differences consistent with the lipophilicity theory, if found, could also relate to drug differences unrelated to lipophilicity. Future studies would be needed to establish which factors are germane.

3. Although we include some of the perceived "susceptible population," specific "high-risk" populations may differ in outcomes from the current population tested. Such potential populations include psychiatric patients, alcoholics, or others at risk from violent effects; or elderly who may be at heightened risk for cognitive effects. Nonetheless, our study is more inclusive in this regard than previous studies and accepts a compromise in completeness of follow-up to allow inclusion of some higher-risk subjects.

4. Measures used may fail to capture effects of interest in the behavioral and cognitive domains. However, we have selected, for primary and secondary analysis, aggression tests shown to correlate with violence and with serotonin; and we have included cognitive measures that were affected by statin treatment in a prior study, reducing the chance that the study will miss an effect if it is present.

5. Although peripheral serotonin measures used may fail to capture effects of treatment on central serotonin, our primary serotonin measure has been shown to correlate with aggression in an unselected birth cohort of humans; and we have included a distinct secondary serotonin measure also linked to aggression, reducing the chance that an important effect on serotonin that could mediate increased aggression will be missed. Our measure has the advantage, if effective, of relative ease of use and identified association with aggression.

6. Measures used may fail to capture effects of interest in the biochemical domain—particularly effects on central serotonin. However, we have selected several measures, some shown to correlate with the central measure cerebrospinal fluid 5-HIAA, which is known to correlate both to cholesterol and to violence, and other serotonin measures shown to correlate with violence in different populations. Although these are less well validated than other measures involving lumbar puncture or drug challenge (with fenfluramine), the fenfluramine option has been forestalled by market withdrawal of this agent for heart valve abnormalities; and lumbar puncture would represent an invasive procedure that would significantly compromise recruitment. We also include as a secondary measure a reactivity test in which heart rate and blood pressure response are assessed, factors previously shown to relate to violence, and provisionally shown to relate to lipids [70–75,117,118]. We employ—on an exploratory basis—secondary measures that are known to relate both to violence or self-harm risk and to serotonin.

7. We incorporate multiple measures; however, we power the study for three main findings and involve a statistician throughout the process from study design to data analysis.

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8. Power may be limited by inclusion of women, for whom an effect of low or lowered cholesterol on violence has not been shown; for whom there is less frequent need for lipid lowering drugs; and for whom violent outcomes are rare. However, inclusion of some women is important because they may not be at lower risk for adverse cognitive effects. Moreover, if reduced serotonin measures are found, these may relate to adverse behavioral or well-being effects in women distinct from overt violence, a matter which will require exploration. To address the potential reduction of power for violent effects by inclusion of women—in whom existing evidence suggests no effect may be seen—the study has been powered for men.

9. Active treatment is split between a hydrophilic statin and a lipophilic one. If effects (such as those on cognition) are not a specific function of serum cholesterol reduction and occur only for lipophilic statins (or exclusively for one statin, for reasons unrelated to lipophilicity), inclusion of both agents may reduce the ability to detect the important effect with one. However, the study was adequately powered to detect an effect from either statin. If an effect is unrelated to lipophilicity, and is statin drug-specific, it is conceivable that effects could occur with other, unstudied statins and not with these. Since CNS effects have been reported with the statins used here, we consider the latter to be unlikely [52,119].

10. The present study does not include the statin currently in widest usage, atorvastatin. Among drugs in use at this writing, it is also the most potent on a milligram basis. If there are selective effects either with this drug, or with higher potency statin use, these effects could be missed.

11. This study does not exclude subjects who are taking SSRIs, in whom the cognitive, behavioral, biochemical, or cardiovascular reactivity effects of lipid lowering therapy may differ, or perhaps be absent. However, we believe patients on SSRIs cannot be excluded from this study because (a) they may in fact constitute a specially vulnerable rather than specially protected population since use of SSRIs is likely to occur selectively in individuals with psychiatric or aggressive predisposition or serotonergic deficit and (b) because this group constitutes a sizable fraction of the population; failure to address the issue in this population would be inappropriate. Without including these individuals in the study, we cannot begin to assess whether they are protected or at heightened risk, and inclusion of these individuals enhances study generalizability. Indeed, because both anger and depression have been shown to enhance risk of coronary and cardiovascular events and fatal events, use of serotonergic agents is being advocated in patients at risk for cardiac events—a population who will also have enhanced likelihood of receiving statin treatment [120–127]. This analysis will allow separate evaluation (exploratory subanalysis) of whether cognitive, biochemical, or reactivity effects are different for subjects receiving SSRIs. Because subjects are not randomized to SSRIs, if differential effects are seen, this study will not address whether some variables strongly associated with selection for use of SSRIs, or effects of SSRIs per se, are responsible for any differences.

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12. The study does not actively select for, or confine analysis to, those at high risk for behavioral or cognitive problems (such as, for behavioral endpoints, those with psychiatric or alcohol problems or noncompliance; for cognitive endpoints, those with histories of head injury or lower baseline cognitive function or education, who are at heightened risk for early diagnosis of Alzheimer's, and older elderly who are at heightened risk for this diagnosis [128]). Such subjects may be at selective risk for adverse effects in these areas: the same change in relative risk may produce a greater change in absolute risk, with more power to demonstrate an effect. In direct analogy, only the statin study employing the highest cardiac risk population among all studies performed showed a significant reduction in cardiac deaths [6]. Nevertheless, the practical, legal, and perhaps ethical issues of focusing study on such a group render that approach unfeasible. Although such subjects are not exempted from treatment with statins, pragmatic issues may render them less likely to receive a prescription or to adhere to treatment, somewhat increasing the generalizability of our findings.

13. The study will not determine the effects of very low LDL-cholesterol or of very large LDL-cholesterol drop, which may occur with some subjects treated with statins in the community. The study employs a lower LDL-cholesterol bound as part of inclusion criteria and uses modest doses of drugs (the LDL-cholesterol-lowering equivalent of 10 mg atorvastatin contrasted with 80 mg of atorvastatin being used in subjects with no lower LDL-cholesterol bound in some studies). Thus, if there is a biological gradient or dose-response effect with impact primarily in those with very low cholesterol, this study could conceivably miss such an effect.

9. Conclusion

This study is the first large controlled trial to address a set of critical issues pertaining to the impact of statins, beneficial or adverse, on noncardiac outcomes including cognition, mood, biochemistry, and quality of life, permitting more authoritative and rigorous evidence to be obtained for a host of questions that have been posed. This will address unresolved issues such as whether statins on average result in benefit or harm to cognitive function, irritability, and serotonin and to secondary outcomes such as sleep, mood, glucose and insulin status, and quality of life. It will also address whether CNS effects, favorable or adverse, are more common or more powerful with use of lipophilic statins, which penetrate more readily into the brain and other tissues than do hydrophilic statins. In addition, it will provide preliminary information regarding whether there are identifiable subsets in whom benefit, or harm, is more likely to be evident. As the scope of the population receiving statins—already the most widely prescribed drugs—continues to expand, the need to secure information on the full spectrum of effects of statins, including the information that this study will provide, is increasingly exigent.

This study is timely in light of recent lipid lowering guideline revisions expanding the scope of eligibility for statins, expected to triple the number who take these agents, to 36 million and in light of the corollary ascendance of statins to the first and second most prescribed of

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all drugs [2,4,5]. It is timely, too, in light of recent attention to noncardiac effects of statins accompanying the withdrawal of cerivastatin (Baycol) from the market for fatal rhabdomyolysis and in light of the recent finding of a 16-fold excess risk of peripheral neuropathy (in a case control study) attending statin use [129–132]. The increasingly widespread use of statins means enormous public health significance may attach to effects of statins, favorable or adverse; and the increasing identification of hitherto poorly recognized adverse as well as beneficial effects of statins underscores the critical need for additional study targeted to more fully understanding the range of effects of statins, so that reasoned risk–benefit decisions can be made [111,133].

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Table 1

Nonlaboratory measures

Test	Baseline	Month 1	Month 3	Month 6	Month 8
	Off treatment	Treatment		Treatment	Off treatment
Intake	+	+	−		+
Cognition					
Grooved pegboard	+	+	−	+	+
Elithorn maze	−	+	−	−	+
Digit symbol	+	+	−	+	+
Digit vigilance	+	+	−	+	+
Hopkins verbal	−	+	−	−	+
Stroop	+	+	−	+	+
Digit span	+	−	−	+	−
Trail making	+	+	−	+	+
ANART	−	−	−	+	−
Behavior					
PSAP	†	†	−	†	†
Conflict tactics	+	+	−	+	+
OAS-M	+	+	−	+	+
Life history of aggression	+	−	−	−	−
SSQ-Conflict	+		−	+	+
Proxy interview, irritability	−	−	+	−	−
Barratt impulsiveness	−	†	−	−	†
Cardiovascular					
Blood pressure, heart rate	−	+	−	+	+
Cardiovascular reactivity	†	−	−	†	−
Mood					
CES-D	+	+	−	+	+
Hospital anxiety	−	†	−	−	†
Wakefield	†	†	−	†	†
Proxy interview, mood	−	−	+	−	−

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Test	Baseline	Month 1	Month 3	Month 6	Month 8
	Off treatment	Treatment		Treatment	Off treatment
Quality of life (QOL)					
SF-12v2	+	+	−	+	+
Symptom survey	+	+	+	+	+
Sleep visual analog	+	+	−	+	+
Overall QOL			−		
Other					
Statin study questionnaire (some questions distributed across visits, e.g., family history)	+	+	−	+	+
Dropouts for cause					
Compliance					
Medication adherence counseling	+	−	+	−	−
Compliance					
MEMSCAP	−	+	+	+	+
Consent, reconsent	+	−	+	−	−
Pill count	−	†	†	†	†
Compliance query	−	†	†	†	†
SSQ conscientiousness					

+: Test done;

−: Test not done;

†: Test performed in a subset.

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Table 2

Laboratory measures

Test	Screening	Baseline	Month 1	Month 3	Month 6	Month 8
Lipid panel	+	+	+	+	+	+
ALT and AST	+	−	−	+	−	−
Renal panel	+	−	−	−	+	−
Whole blood serotonin	−	+	+	−	+	+
Urine 5-HIAA	−	+	+	−	+	+
CBC	−	+	+	−	+	+
Urine cortisol	−	+	+	−	+	+
Glucose	+	+	+	−	+	+
Insulin	−	+	+	−	+	+
Cortisol	−	+	+	−	+	+
Testosterone	−	+	+	−	+	+
Estradiol	−	+	+	−	+	+
GABA	−	+	+	−	+	+
Plasma archive	−	+	+	−	+	+
Tryptophan	−	*	*	−	*	*
Catecholamines	−	†	−	−	†	−
RBC fatty acids	−	+	−	−	+	−
Urine organic acids	−	*	−	−	*	−
Whole blood lead	−	‡	−	−	−	−
Copper	−	‡	−	−	−	−
Zinc	−	‡	−	−	−	−
Buffy coat	−	‡	−	−	−	−
CPK		*	prn if muscle symptoms. Month 6*			

*: tested in a subset. (Tryptophan was scheduled to be tested in all subjects at no cost; issues internal to the laboratory made this no longer possible.)

Lipid panel includes total cholesterol, high-density lipoprotein cholesterol, triglycerides, and low-density lipoprotein cholesterol. ALT=alanine aminotransferase; AST=aspartate aminotransferase; 5-HIAA=5-hydroxyindole acetic acid; CBC=cell blood count; GABA=gamma amino butyric acid; RBC=red blood cell; CPK=creatine phosphokinase.

†: tested in cardiovascular reactivity test subset only.

‡: archived.

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Table 3

Effect sizes detected for primary endpoints[a]

Variable	S.D.	Placebo vs. active drug: effect size detected	Fraction of S.D. for active drug vs. placebo	Simva vs. Prava: effect size detected	Fraction of S.D. detected for Simva vs. Prava
Behavior[b]					
PSAP (aggressions/min)	1.29	0.32	0.247	0.37	0.285
Cognitive function[c]					
Digit vigilance (errors)	04.6	1.36	0.30	1.57	0.34
Recurrent words (% hits)	13.2	3.89	0.30	4.51	0.34
Maze completion (s)	41.0	12.1	0.30	14.0	0.34
Pegboard time (s)	14.2	4.19	0.30	4.86	0.34
Serotonin (5HT)[d]					
Whole blood 5HT (ng/ml)	65.0	16.1	0.247	18.5	0.285

S.D.=standard deviation; Simva=simvastatin; Prava=pravastatin; min=minute; s=seconds; 5HT=5-hydroxytryptamine (serotonin).

[a]Alpha=0.05, two-sided; power of 0.9; *n*=1000.

[b]Data from Dr. D. Cherek.

[c]Data from Dr. M. Muldoon.

[d]Data from Moffitt et al. [61].