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Long-Term Statin Use and Psychological Well-Being

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OBJECTIVES We sought to study the effect of long-term statin use on psychometric measures in an adult population with underlying coronary artery disease (CAD).

BACKGROUND Previous studies have suggested associations between cholesterol lowering and psychological well-being.

METHODS Study subjects were recruited from an outpatient cardiology clinic. Psychological well-being was assessed at baseline and annually during follow-up. The exposure of interest was long-term statin use and the outcomes of interest were depression, anxiety, and hostility. We estimated the odds ratios (ORs) and 95% confidence intervals (CI) that represented the strength of association between statin use (vs. no use of any cholesterol-lowering drug) and the risk of having abnormal depression, anxiety, and hostility scores.

RESULTS Study subjects had an average follow-up of four years and maximum of seven years. Comparing the 140 patients who had continuous use of statins with the 231 patients who did not use any cholesterol-lowering drugs, statin use was associated with lower risk of abnormal depression scores (OR 0.63, 95% CI 0.43 to 0.93), anxiety (OR 0.69, 95% CI 0.47 to 0.99), and hostility (OR 0.77, 95% CI 0.58 to 0.93) after adjustment for the propensity for statin use and potential confounders. The beneficial psychological effects of the statins appeared to be independent of the drugs' cholesterol-lowering effects.

CONCLUSIONS Long-term use of statins among patients with CAD appeared to be associated with reduced risk of anxiety, depression, and hostility. (J Am Coll Cardiol 2003;42:690–7) © 2003 by the American College of Cardiology Foundation

Data from clinical trials have demonstrated strong beneficial effects of the hydroxymethylglutaryl co-A reductase inhibitors (statins) on both primary and secondary prevention of coronary artery disease (CAD) (1–5). The benefits of the statins have even been reported among coronary patients with average serum cholesterol levels (6–8), suggesting that statins have benefits beyond their effect on cholesterol. In addition, the statins appear to exert a wide range of beneficial effects beyond their effect on CAD, including a reduction in the risk of dementia (including Alzheimer's disease) (9–11), stroke (12), macular degeneration (13), and osteoporosis (14–16). With such potential benefits, the use of statins might burgeon well beyond the 36 million (17) patients recently estimated to be eligible for statin therapy according to the guidelines of the National Cholesterol Education Program (NCEP) (18,19). As expanding segments of the population are exposed to statins for prolonged periods, it will be important to gain a more complete understanding of the wide range of effects of statins, including those direct hepatic (cholesterol-lowering) effects and indirect or extra-hepatic effects.

Observations of more than a decade ago suggested that vigorous cholesterol lowering had an adverse impact on psychological well-being (20–27) that included clinical depression, violent behavior, and even suicide. The recent findings of statins' effects on multiple organ systems have given rise to a new interest in their potential psychological effects (28,29). To assess the association between prolonged statin usage and psychological well-being, we reviewed data from a long-term study of an outpatient cohort of individuals with underlying CAD.

METHODS

Study population and data collection. Study subjects were recruited from patients treated at the Lown Cardiovascular Center, an outpatient cardiology referral clinic affiliated with the Brigham and Women's Hospital and Harvard Medical School. Details of the scientific rationale, design, eligibility requirements, and baseline characteristics of the cohort have been published elsewhere (30,31). Consecutive patients with CAD, seen at this clinic from December 1994 and thereafter, were screened and enrolled in a prospective study. Patients were not eligible for enrollment in this longitudinal study if they had undergone prior coronary revascularization (percutaneous or surgical), had moderate to advanced congestive heart failure (New York Heart Association class III or IV), had advanced valvular heart disease, or had severe or life-limiting non-cardiac illnesses. Upon study enrollment, after patients provided informed consent, their sociodemographic, psychological, and clinical data were collected. Thereafter, patients completed annual follow-up questionnaires either at the time of a scheduled clinic visit or by mail. In addition, the cardiologists treating these patients provided clinical data, including medication usage, annually during follow-up. Patient follow-up is

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Abbreviations and Acronyms

CAD = coronary artery disease
GEE = generalized estimating equations
MI = myocardial infarction
SQ = (The Kellner) Symptom Questionnaire

ongoing, and data accrued until June 2001 are included in this report. Average follow-up time was four years, and the longest follow-up was seven years.

Exposure and outcome of interest. Information about medication usage was abstracted from patients' medical records and their annual questionnaires. Cholesterol-lowering drugs were classified as statins (simvastatin, atorvastatin, fluvastatin, lovastatin, cerivastatin, and pravastatin) or non-statin lipid-lowering agents (gemfibrozil, cholestyramine, clofibrate, colestipol, and probucol). Statin usage was the exposure of interest. Patients were divided into three mutually exclusive groups according to statin use during the study period: those who were continuously prescribed statins (always); those who had prescriptions for statins, but not continuously, during the entire study period (intermittent); and those who had never used a cholesterol-lowering drug (never). A fourth group consisting of those who used only non-statin cholesterol-lowering drugs was included at the end of the study for comparison, but it was not included in the primary analysis.

The primary outcomes of interest were anxiety, depression, and hostility as measured by The Kellner Symptom Questionnaire (SQ) (32). At study entry and during their annual physician visits, patients filled out Kellner SQ, Buss-Durkee (33), Cook-Medley (34), Health Locus of Control (HLC) (35,36), as well as Schedule of Recent and Anticipated Experiences (SRE) (37). The Kellner SQ consists of 92 items that yield four scale scores—depression, anxiety, hostility, somatization—and a total distress score. In addition to analyzing these scores as continuous variables, we also classified patients' scores for anxiety, depression, and hostility as "normal" or "abnormal." We dichotomized this continuous outcome because the Kellner scale, like any other scale, is only quasi-continuous and has artificial lower and upper boundary. Moreover, the dichotomization reduces the influence of outliers. Finally, although the cutoff points cannot and should not be used to make psychiatric diagnosis, we wanted to use the categorical changes (normal vs. abnormal) to capture substantial and qualitative changes in addition to the numerical changes. A depression score of seven or above, an anxiety score of eight or above, and a hostility score of eight or above were labeled as abnormal (32).

We chose the Kellner scale as our focus because it measured all three aspects of psychological well-being—anxiety, depression, and hostility. To confirm the reliability and validity of the Kellner scale, we ran additional analyses using Buss-Durkee and Cook-Medley scales. In addition, past major life events and anticipated major future life events were measured using the SRE Questionnaire (37). The HLC scale is an 11-item scale developed to measure personality traits that are related to medical decisions in order to predict health-related behavior. Finally, we recognize the importance of social support and its impact on both psychological well-being and medical decisions, thus we included a composite variable (Social Support) based on the Berkman-Syme Social Network Index (38).

Statistical analysis. Comparisons of psychometric scores were made among the three statin exposure groups (always use, intermittent use, and no cholesterol-lowering drug use). Odds ratios (ORs) and accompanying 95% confidence interval (CI) were calculated to represent the strength of association between statin exposure and abnormal SQ scores for anxiety, depression, and hostility. The generalized estimating equations (GEE) method (39) was used to account for the longitudinal nature of the annually collected data on the exposure of interest (statin use) and outcomes (SQ scores), and logistic GEE models were employed to estimate the corresponding ORs and their 95% CIs. We controlled for baseline characteristics that included age, gender, education (below vs. above college education), use of antidepressants and anxiolytic drugs, history of hypertension, diabetes, myocardial infarction (MI), smoking, regular exercise, alcohol use, past major life events, personality, social support, and total cholesterol level at entry. We also used the GEE model to control for events and changes that occurred during follow-up: changes in total cholesterol level; occurrence of MI; stroke; concomitant use of beta-blockers and calcium channel blockers; cardiac catheterization or revascularization; and anticipated major future life events. More importantly, when we tried to evaluate the psychological effects associated with long-term statin usage, we decided that total number of years of statin use would be inadequate, as some patients would discontinue using statin for a period of time and then resume use of the medication again. As a result, the number of consecutive years of statin use was employed in the present study as a proxy measure for cumulative exposure. Lengths of statin usage were categorized as number of consecutive years of usage, to investigate a potential exposure threshold beyond which reduced abnormal psychometric scoring risk would be observed. The number of consecutive years of statins exposure was evaluated as an independent variable in separate univariate and multivariate models to evaluate the effects of cumulative exposure, with person-time that was not exposed to any cholesterol-lowering drug as the reference group.

We compared not only those who were receiving statin treatment with those who were not receiving any cholesterol-lowering drugs, but also we compared psychometric scores in the same patient while receiving versus while not receiving statin treatment among those patients who had intermittent usage of statins. As a result, some subjects served as their own controls as well as controls for others.

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Table 1. Baseline Characteristics of Study Subjects According to Statin Usage

Statin Usage*	Always	Intermittent	Never
Number of subjects	140	219	231
Age at entry (mean, yrs)	64	66	70
Male (%)	79	83	81
College and above education (%)	65	70	59
Mean blood glucose (mean, mg/dl)	114	117	117
Blood pressure (mean, mm Hg) systolic	134	136	137
Blood pressure (mean, mm Hg) diastolic	77	78	77
Total cholesterol (mean, mg/dl)	206	208	201
HDL cholesterol (mean, mg/dl)	41	38	41
History of smoking (%)	66	68	65
Current smokers (%)	8	5	6
Regular exercise (%)	87	88	82
Beta blockers (%)	71	71	68
ACE inhibitor (%)	10	12	7
Calcium channel blockers (%)	61	52	55
Aspirin (%)	84	81	75
History of catheterization (%)	35	40	31
History of myocardial infarction (%)	41	40	45
History of hypertension (%)	51	57	55
History of diabetes (%)	17	17	12
Depression (SQ) (mean)	6	6	6
Anxiety (SQ) (mean)	7	7	7
Hostility (SQ) (mean)	8	8	8
Health locus of control (mean)	39	40	39
Social support (mean)	4	4	4

*The "Always" group includes those who were on statins throughout the study. The "Intermittent" group includes those who were on statins intermittently throughout the study. The "Never" group includes those who were never on any cholesterol-lowering drugs throughout the study.

ACE = angiotension-converting enzyme; HDL = high-density lipoprotein; SQ = (Kellner) Symptom Questionnaire.

Because statin use was not randomly assigned in this patient population, potential confounding and selection biases were accounted for by developing a propensity score for statin use. Propensity analysis (40) was performed regarding the probability of statin prescription. For each patient, a propensity score indicating the likelihood of having statins prescribed was calculated by multivariate logistic regression analysis (41). The propensity for statin use was determined without regard to outcome. A full non-parsimonious model was developed that included 24 covariates, all of which are listed in Table 1. The multivariate regression model of propensity for statin use had a *c* statistic of 0.86, which represents the area under the receiver operating characteristic curve, indicating a good ability to differentiate between statin users and nonusers. The score ranged from 0.03 to 0.97, representing the probability that a patient would be prescribed statin.

All these variables, together with individual propensity scores, were forced into the logistic GEE models evaluating the association of statin use and psychological well-being. All analyses were carried out using STATA 7.0 (Stata Corporation, College Station, Texas).

RESULTS

Between December 1992 and June 2001, 2,598 men and women of all ages with CAD were screened for enrollment at the Lown Cardiovascular Center; 761 subjects met our study's inclusion criteria and agreed to participate. A total of 606 patients who had at least one year of follow-up, baseline psychometric data, and complete medication information were included in this analysis. As selective attrition could potentially bias the results of our study, we paid special attention to the survey response rate. The response rate for completing the psychometric questionnaires was consistently high—an average of 91%. During follow-up, only 25 subjects (4%) voluntarily withdrew from the study, and 36 subjects (6%) died.

Baseline characteristics of patients in the always-used statins, intermittent use of statins, and no cholesterol-lowering drug use groups were similar, including their psychometric profile (Table 1). Although those who were intermittently using statins had slightly higher levels of total serum cholesterol, their average total cholesterol was not clinically significant according to the NCEP guidelines.

Patients who were using statins showed a trend toward better psychometric scores for depression, anxiety, and hostility as measured by the Kellner scale during follow-up, while there was little change in these scores among those who did not use any cholesterol-lowering drugs (Fig. 1). Additional analyses were performed using other psychometric scales, and similar results were found (not reported). Using the logistic GEE model to account for repeated assessment of statin usage and psychometric scores, we found that those who used statins continuously throughout the study period were significantly less likely to have abnormal depression scores (OR 0.63, 95% CI 0.43 to 0.93), abnormal anxiety scores (OR 0.69, 95% CI 0.47 to 0.99), and abnormal hostility scores (OR 0.77, 95% CI 0.58 to 0.93) (Table 2). The beneficial effects of statin exposure were found after we adjusted for differences in baseline characteristics and clinical events during follow-up, the most important ones being baseline psychometric scores, baseline and change in cholesterol level, and baseline psychosomatic medication usage. Patients who used statins intermittently did not show the same beneficial effects (Table 2).

Employing the number of years of statin use as the exposure of interest and person-years not using any cholesterol-lowering drug as reference, the consecutive years of statin use were associated with a lower risk of having abnormal depression, anxiety, and hostility scores, after adjusting for the potential confounders described above (Fig. 2). After including those who used non-statin cholesterol-lowering drugs, we found that the observed beneficial psychological effects were most prominent among those who used statins in contrast to non-statin cholesterol-lowering drugs (Table 3).

We investigated whether the association between statin use and abnormal psychometric scores depended on baseline serum cholesterol levels and on changes in these levels during follow-up. We examined the risk of developing abnormal psychometric scores according to statin use in

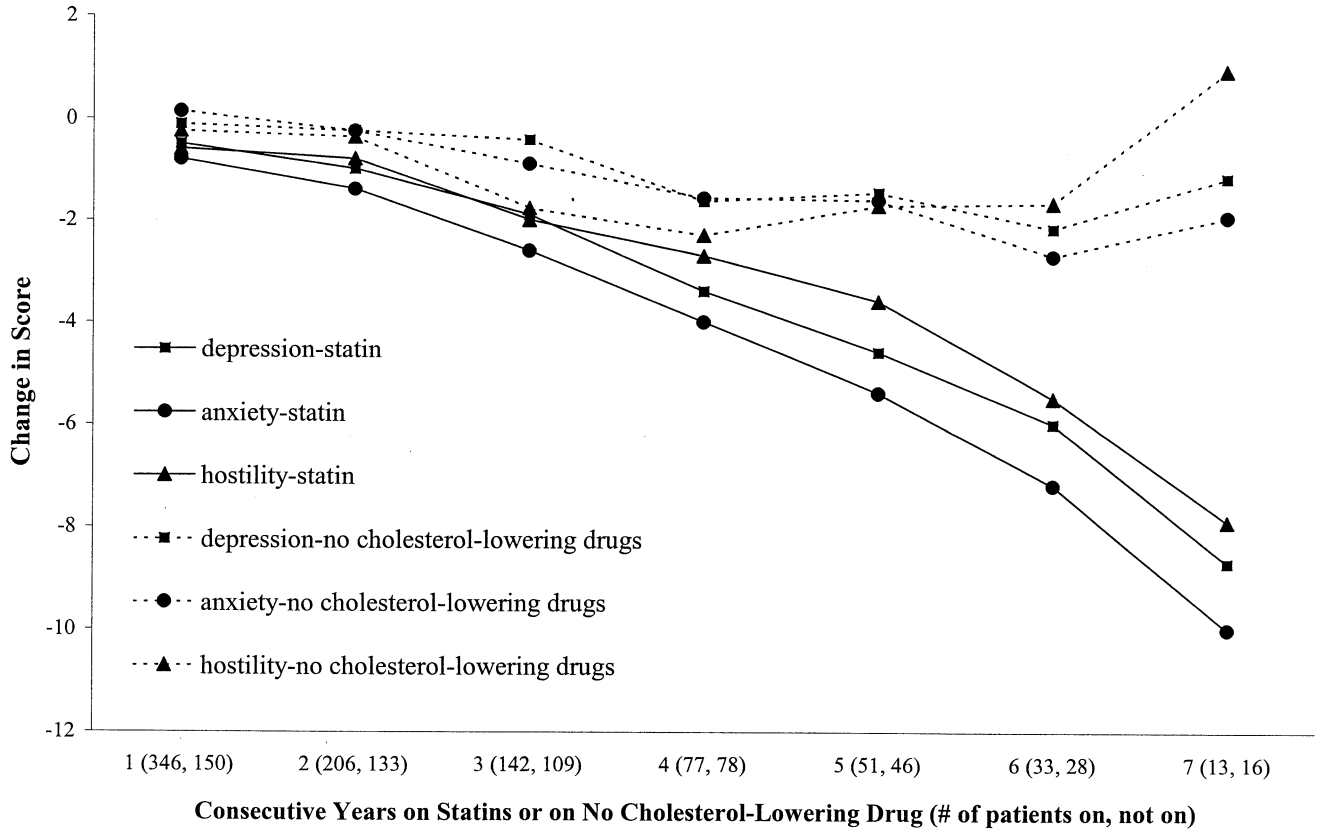

Figure 1. Association between change in Kellner Symptom Questionnaire score and consecutive years of statin use or no use of cholesterol-lowering drugs.

patients with baseline normal (<200 mg/dl), intermediate (200–239 mg/dl), and elevated (≥240 mg/dl) total serum cholesterol levels (Table 4). Furthermore, the study sample was divided into four groups of relatively equal sizes according to the percentage change in total serum cholesterol levels between the time of enrollment and termination of follow-up. Within each of the groups of total cholesterol, and each of the groups of change in total cholesterol, relative risks consistently indicated a reduced likelihood of developing abnormal psychometric scores (Table 4). In a multivariate logistic GEE model, entering cholesterol level and percentage change in cholesterol level separately and then together, we found that the inclusion of these variables did not alter the association between statin use and abnormal psychometric scores.

Table 2. Association of Abnormal Scoring With Statin Usage by Psychometric Scales

Statin Use	Depression	Anxiety	Hostility
Adjusted with propensity*			
Always	0.63 (0.43–0.93)	0.69 (0.47–0.99)	0.77 (0.58–0.93)
Intermittent	0.81 (0.59–1.10)	0.96 (0.71–1.31)	0.94 (0.75–1.19)
Never	referent	referent	referent
Adjusted†			
Always	0.64 (0.43–0.93)	0.62 (0.43–0.90)	0.65 (0.45–0.93)
Intermittent	0.80 (0.59–1.11)	0.92 (0.68–1.24)	0.94 (0.71–1.26)
Never	referent	referent	referent
Crude			
Always	0.66 (0.50–0.86)	0.67 (0.51–0.87)	0.79 (0.62–1.02)
Intermittent	0.86 (0.69–1.06)	0.96 (0.78–1.19)	0.98 (0.80–1.20)
Never	referent	referent	referent

*GEE longitudinal multivariate model with adjustment for propensity as well as age (age − mean age); length of follow-up; gender; education (below vs. above college education); blood glucose level; systolic, diastolic blood pressure; total cholesterol; high-density lipoprotein, heart rate; current smoking; regular exercise; alcohol use; past major life events; anticipated major future life events; use of antidepressants and anti-anxiety drugs at time of enrollment; statin usage prior to study entry; use of beta-blockers, calcium channel blockers at enrollment and during follow-up; history of catheterization, myocardial infarction, hypertension, diabetes; incidence of myocardial infarction, stroke, catherization, revascularization. †Same as above, but not including propensity score.

DISCUSSION

The results of this observational study suggest that long-term statin therapy consistently improves psychological well-being among a cohort of patients with CAD. A progressive, cumulative reduction in the levels of depression, anxiety, and hostility was observed over a prolonged period of statin use. This finding was the outcome of a longitudinal, multivariate analysis that controlled for many potential confounding effects and the propensity for statin prescription. The possible impact on psychometric scores was independent of the serum cholesterol level at baseline and of the degree of reduction in cholesterol level during follow-up.

Several earlier studies (29,42,43) have demonstrated no

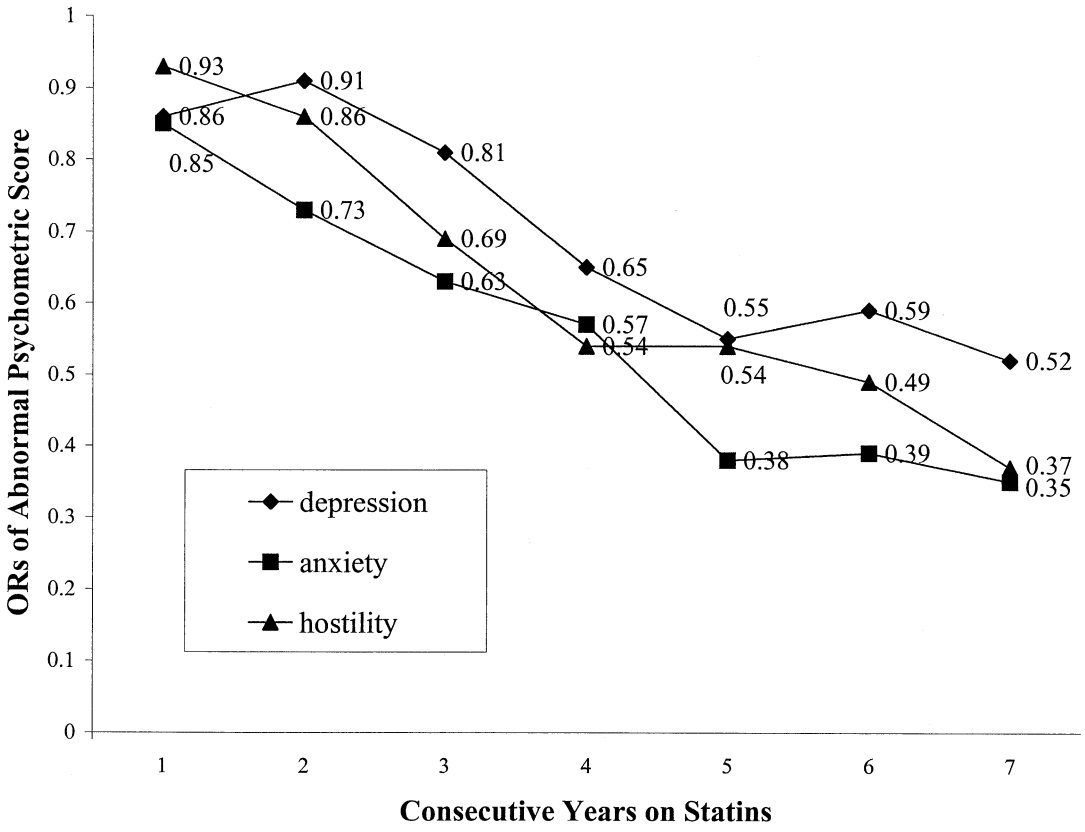

Figure 2. Odds ratios of abnormal psychometric scores and length of consecutive statin usage. *The generalized estimating equations longitudinal multivariate model with adjustment for propensity, as well as age (age minus mean age); length of follow-up; gender; education (below vs. above college education); blood glucose level; systolic and diastolic blood pressure; total cholesterol; high density lipoprotein level; heart rate; current smoking; regular exercise; alcohol use; past major life events; anticipated major future life events; use of antidepressants and anti-anxiety drugs at time of enrollment; statin use prior to study entry; use of beta blockers or calcium channel blockers at enrollment and during follow-up; history of catheterization, myocardial infarction, hypertension, and diabetes; incidence of myocardial infarction, stroke, catheterization, and revascularization.

association between statins and psychological state. Although our findings agree with the results that statins produce no harmful psychological effects, these studies are methodologically different from ours in several important aspects: their study populations were different from ours; their choice of medication was too limited—for example, only hydrophilic statin; and all of their follow-up periods were shorter. We observed changes in the psychometrics

Table 3. Association Between Abnormal Scoring With Cholesterol-Lowering Treatment by Types of Cholesterol-Lowering Drugs

	Person Year	Depression	Anxiety	Hostility
Adjusted*				
All	1,001	0.77 (0.63–0.97)	0.77 (0.62–0.96)	0.79 (0.64–0.98)
Non-statin	133	0.85 (0.33–2.18)	0.81 (0.39–1.85)	0.83 (0.38–1.90)
Statins	868	0.77 (0.61–0.96)	0.75 (0.58–0.97)	0.78 (0.63–0.98)
Hydrophilic	148	0.89 (0.50–1.59)	1.06 (0.64–1.77)	0.87 (0.44–1.35)
Lipophilic	720	0.75 (0.60–0.96)	0.75 (0.59–0.95)	0.78 (0.62–0.98)
Crude				
All	1,001	0.78 (0.65–0.96)	0.74 (0.60–0.91)	0.74 (0.61–0.89)
Non-statin	133	0.92 (0.31–1.66)	0.92 (0.46–1.86)	1.12 (0.53–2.34)
Statins	868	0.78 (0.64–0.96)	0.73 (0.58–0.92)	0.73 (0.58–0.88)
Hydrophilic	148	0.92 (0.55–1.52)	0.98 (0.61–1.57)	0.86 (0.52–1.42)
Lipophilic	720	0.77 (0.63–0.95)	0.72 (0.58–0.89)	0.72 (0.59–0.88)

Data are presented as odds ratio (95% confidence interval). *Generalized estimating equations longitudinal multivariate model with adjustment for age (age − mean age); length of follow-up; gender; education (below vs. above college education); blood glucose level; systolic, diastolic blood pressure; total cholesterol; high-density lipoprotein; heart rate; current smoking; regular exercise; alcohol use; past major life events; anticipated major future life events; use of antidepressants and anti-anxiety drugs at time of enrollment; lipid-lowering agent usage prior to study entry; use of beta-blockers, calcium channel blockers at enrollment and during follow-up; history of catheterization, myocardial infarction, hypertension, diabetes; incidence of myocardial infarction, stroke, catheterization, revascularization.

Table 4. Risk of Abnormal Psychometric Score by Cholesterol and Changes in Cholesterol

Depression		
Total cholesterol at baseline (no.)*	OR (95% CI)	p Value
Cholesterol <200 (255, 59% on statins)	0.73 (0.52–1.02)	0.07
Cholesterol 200–239 (205, 62% on statins)	0.72 (0.49–1.03)	0.06
Cholesterol 240+ (130, 63% on statins)	0.64 (0.39–1.04)	0.07
% Drop in total cholesterol level (no.)†		
>30% (223)	0.59 (0.40–0.89)	0.01
30% to 21% (135)	0.62 (0.31–1.23)	0.17
20% to 11% (138)	0.51 (0.27–0.95)	0.04
10% or less (94)	0.61 (0.43–0.85)	0.01
Anxiety		
Total cholesterol at baseline (no.)*	OR (95% CI)	p Value
Cholesterol <200 (255, 59% on statins)	0.69 (0.50–0.95)	0.02
Cholesterol 200–239 (205, 62% on statins)	0.68 (0.50–0.94)	0.02
Cholesterol 240+ (130, 63% on statins)	0.71 (0.39–1.31)	0.28
% Drop in total cholesterol level (no.)†		
>30% (223)	0.60 (0.39–0.92)	0.02
30% to 21% (135)	0.74 (0.49–1.12)	0.15
20% to 11% (138)	0.68 (0.46–0.99)	0.05
10% or less (94)	0.90 (0.59–1.37)	0.63
Hostility		
Total cholesterol at baseline (no.)*	OR (95% CI)	p Value
Cholesterol <200 (255, 59% on statins)	0.73 (0.55–0.96)	0.03
Cholesterol 200–239 (205, 62% on statins)	0.69 (0.50–0.96)	0.03
Cholesterol 240+ (130, 63% on statins)	0.84 (0.55–1.29)	0.43
% Drop in total cholesterol level (no.)†		
>30% (223)	0.73 (0.48–1.10)	0.13
30% to 21% (135)	0.72 (0.47–1.09)	0.12
20% to 11% (138)	0.73 (0.50–1.05)	0.09
10% or less (94)	0.85 (0.59–1.23)	0.39

*Serum cholesterol level at entry was grouped by clinically relevant cutoff points. The numbers in parentheses are the number of study subjects in each category. †Changes in cholesterol level were measured by taking the difference between the cholesterol level at entry and at the end of follow-up for each patient.
CI = confidence interval; OR = odds ratio.

only after a full year of statin treatment. It is possible that a longer period of exposure to statins is required to generate an observable impact (Fig. 1).

A number of methodological issues need to be considered when interpreting our findings. The Kellner questionnaire is well validated for detecting change in depression, anxiety, and hostility over time (32). Nevertheless, complex social constructs, such as psychological well-being, have no universally agreed upon definition or measure, and the cutoff points used to define abnormal depression, anxiety, and hostility may not be sufficient to determine completely the psychological state of an individual (32). The Kellner SQ has been shown in both cohort studies and clinical trials to discriminate the effects of different medical treatments. Based on longitudinal studies of psychiatric patients, changes in score were found to correspond with the changes in rating made by psychiatrists using standard psychiatric rating scales (32). To ensure the validity of the Kellner scale in our study, we performed additional analyses, including the Buss-Durkee and Cook-Medley scales, and found similar results (not shown).

Study limitations. A prospective cohort study is subject to loss of study subjects due to follow-up. In this study, the more depressed, more anxious, or more hostile subjects might be more likely to drop out of the study or not fill out their questionnaires. However, it is highly unlikely that the loss to follow-up occurred preferentially among regular statin users, and our very high response rate is not likely to generate substantial information bias. The possibility that physicians withhold statins from those patients who are more depressed or anxious is very doubtful, as statins were prescribed based purely on cardiovascular conditions.

Compliance with the prescription of statins as well as other cardiac drugs has been studied (44). It was found that lipid-lowering drugs in general had a higher rate of compliance (88%) than other cardiac medicines. Moreover, noncompliance would lead to misclassification, which would bias the results towards the null and therefore tend to underestimate the association.

Although statins have become the standard treatment for hypercholesterolemia over the past decade, they did not achieve their current status until the latter half of the 1990s. Our study began in 1992, at a time when prescribing a statin was not as routine as it has become. Instead of medicine, patients were often placed on an exercise and/or a diet program. Our data suggest that the proportion of patients being prescribed statins indeed has been steadily on the rise without significant change in the clinical characteristics of the patients. Moreover, statins increasingly were prescribed for preventive purposes in patients with normal baseline serum cholesterol levels. Because of the steadily declining threshold for statin treatment, some patient who were not initially receiving statins began statin therapy during the study. Nevertheless, some patients stopped taking statins because of side effects and tried other medication and/or diet/exercise programs. These were the main reasons for intermittent use of statins.

We performed propensity analyses to minimize confounding. A propensity score was included in all multivariate logistic GEE models to reduce confounding by factors associated with statin treatment as well as with improved psychological well-being. Using this approach, we found that the main results were similar in all subgroup analyses (Table 2), suggesting that the observed improvement in psychological well-being was related to statin treatment rather than patient selection.

We controlled for many potential confounders, except for non-cardiovascular co-morbidity. Patients with severe or life-limiting noncardiac illnesses were excluded from study entry. Although co-morbidities can be independent risk factors for depression, anxiety, and hostility, they are unlikely to be associated with an exposure to the statins—unless related to hepatic impairment. Concomitant medications, particularly those drugs that affect the central nervous system or other drugs that may have a psychological impact, may be associated with psychological well-being, but we found no association between prescriptions for

antidepressants, anxiolytics, beta-adrenergic blocking agents, calcium-channel blocking agents, and prescriptions for statins. There was no material change in the findings after we controlled for baseline usage of antidepressants and/or anxiolytic drugs. Any unmeasured confounders that would generate a spurious association would have to be a strong predictor of psychological outcomes and affect the choice of statins over no treatment. However, the treatment decision was based solely on a patient's cardiovascular disease risk profile, and the prospectively assessed variables have already been controlled for in the statistical model.

This study has several strengths in comparison to previous studies. The cohort was relatively large and spans the longest follow-up time reported to date. The study also included all the statins rather than just one at a time, as in previous studies. We took into account significant social, medical, and financial life events. Furthermore, we adjusted for cardiac events (MI, stroke, coronary catheterization, and revascularization), exercise, education, smoking, and alcohol consumption, in addition to medication, cholesterol profile, and clinical characteristics.

Our observational study aims to generate further hypotheses and interest in the psychological impact of the statin drugs and in no way should influence how statins are prescribed. The lipophilic statins, as opposed to all other cholesterol-lowering drugs, appear primarily responsible for the observed effect on psychological well-being. Because of the small number of patients treated only with hydrophilic statins or non-statin cholesterol-lowering drugs, we cannot rule out the role of chance, but we hypothesize that the penetration of the blood-brain-barrier by the lipophilic statins accounts for most of the observed impact on psychological well-being. This hypothesis requires further testing.

Conclusions. Psychometric instruments administered annually for up to seven years revealed a progressive reduction in levels of depression, anxiety, and hostility in CAD patients continuously treated with statins. This effect appears to be independent of the impact of statin use on serum cholesterol level.

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