Statin Use and Risk of Depression in Patients With Coronary Heart Disease: Longitudinal Data From the Heart and Soul Study

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ABSTRACT

Background: Statins are among the most commonly prescribed medications worldwide. Although their benefits for cardiovascular disease are well established, the effects of statins on depressive symptoms are unknown.

Method: We examined the association between baseline statin use (2000–2002) and subsequent depressive symptoms in a prospective cohort study of 965 outpatients with coronary disease from 12 outpatient clinics in the San Francisco Bay Area. Depressive symptoms were assessed annually for 6 years using the Patient Health Questionnaire (PHQ) (primary outcome measure). We evaluated the cross-sectional association between statin use and risk of depressive symptoms at baseline and the longitudinal association between baseline statin use and risk of depressive symptoms during follow-up.

Results: Of the 965 participants, 629 (65%) used statins. At baseline, statin users had lower mean ± SE PHQ depression scores than nonusers (4.8 ± 0.2 vs 5.9 ± 0.3, $P < .01$). Statin users were less likely than nonusers to have depression (PHQ score ≥ 10) at baseline (17% vs 24%; $P = .02$) and during follow-up (28% vs 40%; $P < .01$). Among the 776 patients without depressive symptoms at baseline (PHQ < 10), statin use was associated with a 48% decreased odds of developing depression during follow-up (odds ratio [OR], 0.52; 95% CI, 0.38–0.73; $P < .01$). After we adjusted for potentially confounding variables, statin use remained associated with a 38% decreased odds of subsequent depression (adjusted OR, 0.62; 95% CI, 0.41–0.95; $P = .02$).

Conclusions: We found that statin use was associated with a decreased risk of subsequent depressive symptoms in patients with coronary heart disease. Whether use of statins prevents depressive symptoms deserves further study.

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Hydroxymethylglutaryl-CoA reductase inhibitors (statins) are the most commonly prescribed medications worldwide.[1,2] In the United States alone, an estimated 36 million patients are eligible for statin therapy for the primary or secondary prevention of coronary heart disease.[3] Use of statins may also exert a wide range of other beneficial effects, such as reduction in the risk of stroke,[4,5] osteoporosis,[6–8] and certain cancers.[9] In addition, given the immune hypothesis of major depression,[10] statins might exert antidepressive effects by their immunomodulatory effects.[11]

However, the potential effect of statin therapy on psychological well-being has been a subject of substantial controversy. A meta-analysis[12] of early primary prevention studies suggested that patients receiving (nonstatin) cholesterol-lowering therapy may have an increased risk of death from accidents, suicide, or violence. However, 2 large case-control studies[13,14] and 1 prospective study[15] of 371 patients with coronary heart disease have suggested that statin use may be associated with a decreased risk of depression. A potentially preventive effect of statins on depression in patients with cardiovascular disease could be of great importance to public health. To evaluate the association between statin use and depressive symptoms, we assessed statin use in 965 outpatients with stable coronary heart disease and measured depressive symptoms annually for 6 years.

METHOD

Participants

Details regarding our recruitment procedures have been published previously.[16–18] We used administrative databases to identify outpatients with documented coronary disease at 2 Veterans Affairs Medical Centers (San Francisco VA Medical Center and the VA Palo Alto Health Care System, California [n = 438]), 1 university medical center (University of California, San Francisco [n = 346]), and 9 public health clinics in the Community Health Network of San Francisco (n = 240). Patients were eligible to participate if they had at least 1 of the following: a history of myocardial infarction, angiographic evidence of ≥ 50% stenosis in 1 or more coronary vessels, prior evidence of exercise-induced ischemia by treadmill or nuclear testing, or a history of revascularization. From 2000 through 2002, a total of 1,024 participants enrolled and completed a baseline study appointment. All baseline study appointments were conducted at the San Francisco VA Medical Center. Of these, 59 (5.8%) died during the first year of follow-up, leaving 965 participants who provided 2 or more annual measures of depressive symptoms for this analysis. Our protocol was approved by the appropriate institutional review boards. After a complete description of the study to the subjects, written informed consent was obtained.

Statin Use

All participants brought their medication bottles to the baseline study appointment, and study personnel recorded all medications including statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, or simvastatin).

Clinical Points

- Although beneficial effects of statins for cardiovascular disease are well established, their effects on depressive symptoms are unknown.
- In this study of patients with coronary heart disease, use of statins was associated with a decreased risk of exhibiting depressive symptoms both in cross-sectional and longitudinal analyses.
- In patients free of depressive symptoms at baseline, statin use at baseline was associated with a 38% reduced risk of developing depression during 6 years of follow-up.

Depressive Symptoms

Depressive symptoms were assessed annually for 6 years (2000–2002 through 2005–2007) using the 9-item Patient Health Questionnaire (PHQ),[19] a self-report instrument that measures the frequency of depressive symptoms corresponding to the 9 *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition criteria for major depressive disorder. A paper-and-pencil version of the PHQ was administered at the baseline examination; telephone versions were administered after 1, 2, 3, and 4 years of follow-up; and a paper-and-pencil version was again administered after the fifth year of follow-up. At each assessment, participants were asked to indicate the frequency of experiencing each of 9 symptoms during the last 2 weeks. The instrument was scored as not at all (0), several days (1), more than half the days (2), or nearly every day (3), with a total score range of 0 to 27.

We evaluated depressive symptoms both as a continuous variable (range, 0–27) and as a dichotomous variable using the standard cut-off point of 10 or higher.[20] Using a cut point of 10, the PHQ has demonstrated excellent validity when compared with a structured diagnostic interview for depression in patients with coronary artery disease.[21] Telephone and in-person PHQ assessments yield similar results.[22] Of the 965 participants, 137 participants died during the follow-up period. A total of 756 participants completed 5 or more annual assessments, 99 completed 4 assessments, 70 completed 3 assessments, and 40 completed 2 assessments.

Participants who completed at least 80% of possible assessments while still alive (n = 816) did not differ in baseline depression scores, statin use, or antidepressant use from those completing less than 80% of possible assessments (n = 146).

Other Patient Characteristics

Age, sex, alcohol use, medical history, and smoking were determined by self-report. Body mass index was calculated as weight in kilograms divided by the square of height in meters. All participants underwent resting echocardiography using an Acuson Sequoia ultrasound system (Mountain View, California). We obtained standard 2-dimensional views and performed planimetry with a computerized digitization system to determine left ventricular ejection fraction.[23] Participants also completed an exercise treadmill test according to a standard Bruce protocol at the baseline examination. Those who were unable to continue the standard Bruce protocol were switched to slower settings and encouraged to exercise for as long as possible. Exercise capacity was calculated as the total number of metabolic equivalent tasks achieved. Fasting blood samples were drawn for measurement of lipids and high-sensitivity C-reactive protein.

Statistical Analysis

The goal of this study was to examine the association of statin use with depressive symptoms in patients with coronary heart disease. Differences in characteristics between statin users and nonusers were compared using univariate analysis of variance for continuous variables and χ^2 tests for dichotomous variables. C-reactive protein was log transformed because it did not have a normal distribution. We used logistic regression to evaluate the association between statin use and presence of baseline depressive symptoms (PHQ score ≥ 10), adjusting for potentially confounding variables.

We used generalized linear mixed models (GLIMMIX procedure) to examine the longitudinal association between statin use at baseline and depressive symptoms during the follow-up period at any time point. To account for possible confounding, we constructed multivariable models adjusted for age, sex, smoking, medical history, use of other medications, C-reactive protein, non–high-density lipoprotein (HDL) cholesterol, exercise capacity, baseline depressive symptom score, and recruitment site. We also repeated all analyses in participants who were initially free of depressive symptoms (baseline PHQ score < 10). Analyses were performed using Statistical Analysis Software (SAS version 9.2; SAS Institute, Cary, North Carolina).

RESULTS

At baseline, 629 of 965 participants (65%) used statins. As compared with nonusers of statins, participants using statins were older, more likely to be male, less likely to smoke, more likely to be adherent to medication, and less likely to have a low income (Table 1). Statin users were more likely to have a history of myocardial infarction, stroke, diabetes, hypertension, and heart failure and to be treated with angiotensin-converting enzyme (ACE) inhibitors and β-blockers. Statin use was associated with better exercise capacity, lower non-HDL cholesterol, and lower C-reactive protein values.

Statin Use and Depressive Symptoms at Baseline

Statin users had lower mean ± SE PHQ depression scores than nonusers (4.8 ± 0.2 vs 5.9 ± 0.3, $P < .01$), and this association remained significant after adjustment for age, sex, smoking, education, income, social support, medical history, use of β-blockers, angiotensin receptor blockers, C-reactive protein, non-HDL cholesterol, exercise capacity,

Table 1. Characteristics of Participants According to Statin Use at Baseline[a]

Demographic	Statin Use (n = 629)	No Statin Use (n = 336)	*P* Value
Age, y	67.5 ± 10.0	65.1 ± 11.9	< .01
Male gender, n (%)	530 (84)	253 (75)	< .01
Body mass index	28.7 ± 4.9	28.3 ± 6.0	.27
Smoking, n (%)	102 (16)	84 (25)	< .01
High school graduate, n (%)	549 (87)	290 (86)	.67
Low income (< $20,000), n (%)	277 (44)	191 (57)	< .01
Living alone, n (%)	210 (33)	124 (37)	.29
Poor social support, n (%)	205 (33)	108 (32)	.91
Nonadherence, n (%)	38 (6.1)	40 (12.2)	.001
Medical history, n (%)			
Myocardial infarction	360 (58)	155 (47)	< .01
Stroke	99 (16)	37 (11)	.04
Diabetes	178 (28)	66 (20)	< .01
Hypertension	467 (74)	218 (65)	< .01
Congestive heart failure	122 (19)	45 (13)	.02
History of depression, n (%)	170 (27)	115 (34)	.02
Medication use, n (%)			
Angiotensin receptor blocker	370 (59)	123 (37)	< .01
β-blocker	429 (68)	138 (41)	< .01
NSAID use	107 (17.0)	68 (20.2)	.215
Selective serotonin reuptake inhibitor	57 (9)	34 (10)	.59
Any antidepressant	108 (17)	65 (19)	.40
Cardiac function			
Exercise capacity (METs)	7.6 ± 3.2	7.1 ± 3.4	.04
Left ventricular ejection fraction	0.62 ± 0.10	0.63 ± 0.10	.12
Laboratory			
HDL cholesterol, mmol/L	45 ± 14	47 ± 15	.15
Non-HDL cholesterol, mmol/L	124 ± 34	148 ± 47	< .01
Triglyceride, mmol/L	139 ± 122	146 ± 143	.43
Log C-reactive protein	0.6 ± 1.3	0.9 ± 1.4	< .01

[a]All values are mean and standard deviations except where indicated.
Abbreviations: HDL = high-density lipoprotein, METs = metabolic equivalent tasks, NSAID = nonsteroidal anti-inflammatory drug.

Table 2. Association of Statin Use With Depressive Symptoms (PHQ score ≥ 10) at Baseline

Variable	OR (95% CI)	*P* Value
Model 1[a]	0.68 (0.50–0.93)	.02
Model 2[b]	0.67 (0.47–0.94)	.02
Model 3[c]	0.63 (0.43–0.91)	.02
Model 4[d]	0.65 (0.45–0.95)	.03
Model 5[e]	0.65 (0.44–0.96)	.03
Model 6[f]	0.66 (0.45–0.98)	.04

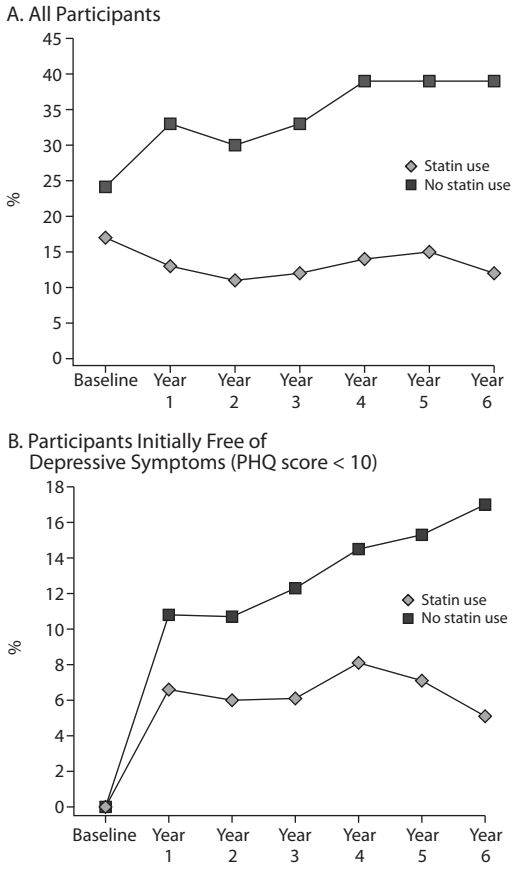
[a]Unadjusted.
[b]Adjusted for age, sex, smoking, history of myocardial infarction, diabetes, stroke, hypertension, congestive heart failure.
[c]Adjusted for all variables in model 2 plus use of β-blocker, use of angiotensin receptor blocker, C-reactive protein, and non–high-density lipoprotein cholesterol.
[d]Adjusted for all variables in models 2 and 3 plus site.
[e]Adjusted for all variables in models 2 through 4 plus education, income, living alone, social support.
[f]Adjusted for all variables in model 2 through 5 plus nonadherence.
Abbreviation: PHQ = Patient Health Questionnaire.

nonadherence, and recruitment site (5.1 ± 0.3 vs 5.9 ± 0.3; *P* < .01). When depression was evaluated as a dichotomous variable (PHQ score ≥ 10), statin users were less likely to have depression than nonusers (17% vs 24%, *P* = .02; Table 2).

Statin Use and Depressive Symptoms During Follow-Up

In repeated-measures models, baseline statin use was strongly predictive of subsequent PHQ depression scores as a continuous variable (β coefficient = −1.22, *P* ≤ .01). This

Figure 1. Depressive Symptoms According to Statin Use at Baseline[a]



[a]Proportion of patients with depressive symptoms (PHQ score ≥ 10) during 6 years of follow-up according to statin use at baseline.
Abbreviation: PHQ = Patient Health Questionnaire.

association remained strong after adjustment for age, sex, smoking, education, income, social support, medical history, use of β-blockers, ACE inhibitors, C-reactive protein, non-HDL cholesterol, exercise capacity, baseline depressive symptoms score, and recruitment site (β coefficient = −0.45, *P* = .02). When depression was evaluated as a dichotomous variable (PHQ score ≥ 10), users of statins were less likely than statin nonusers to have depression once or more during follow-up (28% vs 40%, *P* < .01; Figure 1A). After multivariable adjustment, statin use remained associated with a 33% decreased odds of having depression during follow-up (OR = 0.67; 95% CI, 0.48–0.92; *P* = .015; Table 3). There was no significant difference in depression during follow-up among patients who did or did not continue using statins (*P* > .40). Furthermore, there were no differences between those who died (n = 137) versus those who did not die during follow-up (n = 828) with regard to depressive symptoms at baseline (*P* > .30) or statin use at baseline (*P* > .15).

Subgroup Without Depressive Symptoms at Baseline

Among the 776 participants who were free of depressive symptoms at baseline (PHQ score < 10), statin use was strongly predictive of subsequent depressive symptom scores

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Table 3. Association of Statin Use With Subsequent Depressive Symptoms (PHQ ≥ 10 once or more during follow-up) Among All Study Participants and Among Those Without Depressive Symptoms at Baseline (PHQ score < 10)

	All Study Participants (n = 965)		Participants Without Depressive Symptoms at Baseline (n = 776)	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Model 1[a]	0.53 (0.40–0.79)	< .01	0.52 (0.38–0.73)	< .01
Model 2[b]	0.63 (0.48–0.84)	< .01	0.60 (0.43–0.84)	< .01
Model 3[c]	0.60 (0.46–0.79)	< .01	0.56 (0.39–0.81)	< .01
Model 4[d]	0.61 (0.46–0.81)	< .01	0.56 (0.38–0.82)	< .01
Model 5[e]	0.66 (0.48–0.91)	.01	0.61 (0.40–0.91)	.02
Model 6[f]	0.66 (0.48–0.91)	.01	0.60 (0.40–0.91)	.015
Model 7[g]	0.65 (0.47–0.91)	.01	0.60 (0.40–0.91)	.015
Model 8[h]	0.67 (0.48–0.92)	.015	0.62 (0.41–0.95)	.026

[a]Unadjusted.
[b]Adjusted for age, sex, and smoking.
[c]Adjusted for all variables in model 2 plus age, sex, smoking, history of myocardial infarction, diabetes, stroke, hypertension, congestive heart failure, and baseline depressive symptoms score.
[d]Adjusted for all variables in models 2 and 3 plus use of β-blocker, use of angiotensin receptor blocker, C-reactive protein, and non–high-density lipoprotein cholesterol.
[e]Adjusted for all variables in models 2 through 4 plus baseline treadmill exercise capacity.
[f]Adjusted for all variables in models 2 through 5 plus site.
[g]Adjusted for all variables in models 2 through 6 plus education, income, living alone, and social support.
[h]Adjusted for all variables in models 2 through 7 plus nonadherence.
Abbreviation: PHQ = Patient Health Questionnaire.

(fully adjusted β coefficient = −0.48, *P* = .01). Among nondepressed participants, statin users were less likely to develop depression (PHQ score ≥ 10) once or more during follow-up than statin nonusers (18% vs 28%, *P* < .01; Figure 1B). After multivariable adjustment, statin use remained associated with a 40% decreased odds of developing depressive symptoms during follow-up (fully adjusted OR = 0.62; 95% CI, 0.41–0.95; *P* = .026; Table 3).

DISCUSSION

In this prospective cohort study of 965 outpatients with stable coronary heart disease, we found that statin use was associated with a decreased risk of depressive symptoms during 6 years of follow-up. Even after adjusting for age, sex, smoking, education, income, social support, baseline depressive symptoms, comorbid illnesses, concomitant medication use, C-reactive protein, non-HDL cholesterol, treadmill exercise capacity, nonadherence, and recruitment site, statin use remained associated with a 34% decreased odds of depressive symptoms during follow-up. Among participants free of depression at baseline, statin use was associated with a 38% decreased odds of developing depression.

Our findings raise the possibility that statins may prevent depressive symptoms in patients with cardiovascular disease. The 34%–38% decreased odds of depression is remarkably similar to the 37% decreased odds of depression observed in the only other prospective study cohort study evaluating the association between statin use and depression in patients with coronary heart disease.[15] Our results are also consistent with 2 large, retrospective, case-control studies using administrative databases reporting the same magnitude of association between statin use and reduced risk of depression in a more general patient population.[13,14]

To date, however, randomized trials have failed to demonstrate a beneficial effect of statin therapy on psychological well-being.[24–27] In 1 randomized trial[27] of 1,130 patients with existing coronary heart disease, those assigned to pravastatin had lower subsequent depression scores (measured by the General Health Questionnaire) during 4 years of follow-up than those assigned to placebo, but these differences were not statistically significant. Another trial[24] in individuals with hyperlipidemia but without known coronary artery disease found no improvement of depressive symptoms (measured by the Profile of Mood States) during almost 3 years of follow-up among patients assigned to simvastatin versus those assigned to placebo. Likewise, 2 short-term trials[25,26] in individuals with hyperlipidemia but without overt coronary artery disease found no significant effect of statin therapy on depressive symptoms during 6 months of follow-up. Only 1 small pilot trial[28] has demonstrated an improvement in depressive symptoms associated with statin use in hyperlipidemic patients during 1 year of follow-up.

There are several potential explanations for these observed differences in the results of observational studies and randomized trials. One possibility is a user bias in which patients who take statins may be more likely to exhibit other healthy behaviors that would decrease their risk of depression. Indeed, we found that statin use was also associated with less smoking, higher income, better exercise capacity, concomitant use of other cardio-protective medications, better cholesterol, and lower C-reactive protein levels. However, even after adjustment for these and other factors, statin use remained associated with decreased odds of depression. Furthermore, baseline statin use was associated with a history of myocardial infarction, stroke, diabetes, hypertension, and heart failure, making user bias less likely. Finally, we found the same magnitude of association between statin use and decreased odds of developing depression over time when we restricted our analyses to initially nondepressed patients.

Another possibility is that a larger sample size is necessary to demonstrate a beneficial effect of statins on depressive symptoms. Of note, our study included more statin users (n = 629) than any of the previous observational studies or randomized trials. In addition, none of the randomized trials were specifically designed to evaluate depressive symptoms, and more precise measurement of depressive symptoms (rather than use of general well-being questionnaires) may be necessary to detect an effect. Further, if improvements in depressive symptoms are long-term effects of statins, then trials of longer duration may be required to demonstrate benefit. Finally, it is possible that the effects of statins on depression depend on the patient group examined. Most of the randomized trials have been conducted in hyperlipidemic patients without coronary heart disease. The only trial that did examine coronary heart disease patients used a general well-being scale.[27] This contrasts with our and the previous

observational study[15] demonstrating an almost identical association between statin use and reduced risk of depression in patients with coronary heart disease. Therefore, future studies should examine the effects of statin use on depression in different patient populations of sufficient sample size over a longer period of time using scales specific for depression.

The potential mechanisms by which statins might be beneficial on depressive symptoms are unclear. It is possible that statins exert beneficial effects on depressive symptoms through protective effects on cerebrovascular processes. Indeed, it has been shown that statins have a number of direct vasoprotective effects and may reverse endothelial dysfunction.[29] This includes their immunomodulatory effects.[11] Consistent with this hypothesis, the previous observational studies found beneficial effects of statins on depressive symptoms in patients with cardiovascular disease only after a full year of statin treatment. The effects further increased with every year of statin use[15] and, in our study, the largest difference between statin users and nonusers became apparent after 6 years of follow-up. This hypothesis is also consistent with our findings in the subsample of initially nondepressed patients. In these participants, use of statins might have exerted protective effects with regard to the development of vascular depression.[30]

Our study has several strengths, including detailed assessment of baseline cardiac disease severity, annual assessment of depressive symptoms using established instruments, adjustment for potential confounding variables, and a large sample size with more than 85% of participants completing at least 80% of possible follow-up assessments. However, several limitations must also be considered. First, most of our participants were older men, and almost half were recruited from VA medical centers. Therefore, our results may not generalize to women or to other patient populations. Second, it is possible that some misclassification of statin use may have occurred. However, misclassification would bias the results toward null. Third, lipid values prior to statin use and length of statin use prior to study entry were not available and, therefore, we do not know whether the association between statin use and reduced risk of depression was mediated by changes in lipid levels. However, in the previous observational study of patients with coronary heart disease, the beneficial effects of statins on depression appeared to be independent of lipid-lowering effects.[15] Fourth, our study was limited to outpatients with stable coronary heart disease, and thus we cannot comment on the association between statin use and depressive symptoms in healthier populations. Fifth, statin users were less likely than nonusers to report a history of depression. However, our results remained stable in multivariable analyses adjusted for baseline depressive symptoms and repeated in the subgroup of patients without baseline depressive symptoms. Nevertheless, we had no information on chronicity of depressive symptoms or dysthymia prior to study entry. Finally, our observational data cannot infer causality, which would need to be proven by a randomized controlled trial. However, given that statins are recommended for secondary prevention, it would not be possible to randomize patients with established coronary heart disease to placebo.

In summary, we found that statin use was associated with a 34% decreased odds of exhibiting depressive symptoms during 6-year follow-up after adjusting for potential confounding variables in patients with coronary heart disease. Among participants free of depression at baseline, statin use was associated with a 38% decreased odds of developing depression. The potential mechanisms by which statins may prevent depressive symptoms deserve further study.

Drug names: atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Altoprev, Mevacor, and others), pravastatin (Pravachol and others), rosuvastatin (Crestor), simvastatin (Zocor and others).

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Author contributions: Dr Whooley had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Potential conflicts of interest: **Dr Otte** is on the speaker's board of AstraZeneca, Lundbeck, and Servier. **Dr Zhao** and **Dr Whooley** report no conflicts of interests.

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