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Hepatic Effects of Lovastatin Exposure in Patients with Liver Disease

A Retrospective Cohort Study

Andrew L. Avins,[1,2,3,4] *Michele M. Manos*,[1,3] *Lynn Ackerson*,[1] *Wei Zhao*,[1] *Rosemary Murphy*,[1] *Theodore R. Levin*,[1] *Douglas J. Watson*,[5] *Peggy M.T. Hwang*,[5] *Amy Replogle*[5] and *Jeffrey G. Levine*[5]

1 Kaiser Permanente Division of Research, Oakland, California, USA
2 Department of Medicine, University of California, San Francisco, USA
3 Department of Epidemiology & Biostatistics, University of California, San Francisco, USA
4 Veterans Affairs Medical Center, San Francisco, California, USA
5 Merck & Co., West Point, Pennsylvania, USA

Abstract

Background: Little is known about the potential adverse hepatic effects of HMG-CoA reductase inhibitors ('statins') in patients with existing liver disease; therefore, we examined the risk of liver toxicity with lovastatin exposure in these patients.

Methods: A retrospective cohort study was performed using data from a large integrated health plan in Northern California, USA. Patients with laboratory or clinical evidence of liver disease were identified and their exposure to lovastatin was determined. The primary outcome was a pattern of liver-test abnormalities associated with a poor prognosis among patients with drug-induced liver disease, based on Hy's Rule. Secondary outcomes included liver injury (defined as moderate or severe, depending on the degree of ALT level elevations) or the development of either clinical cirrhosis or liver failure. Incidence rate ratios (IRRs) were calculated and multivariate analyses conducted using extended Cox models.

Results: A total of 93 106 patients met the entry criteria. Lovastatin exposure was associated with a lower incidence of all endpoints, including the primary outcome (IRR = 0.28, 95% CI 0.12, 0.55), moderate liver injury (IRR = 0.56, 95% CI 0.47, 0.65), severe liver injury (IRR = 0.50, 95% CI 0.29, 0.81) and the occurrence of either cirrhosis or liver failure (IRR = 0.29, 95% CI 0.21, 0.38); adjustment for age and sex resulted in some attenuation of this reduction in incidence. The observed effects were generally consistent across a range of baseline liver-disease diagnoses and greater cumulative lovastatin exposure was associated with fewer outcome events for some endpoints.

Conclusions: In this retrospective analysis, exposure to lovastatin was not associated with an increased risk of adverse hepatic outcomes. These results do not support concern regarding lovastatin-related hepatotoxicity in patients with existing liver disease.

Introduction

The HMG-CoA reductase inhibitors ('statins') are effective in reducing coronary heart disease risk in both primary and secondary prevention.[1-6] Limiting the wider use of these agents, however, is the concern regarding their potential adverse effects, primarily rhabdomyolysis and liver toxicity. Rhabdomyolysis has been firmly linked to the use of statins and interacting medications,[7] while the association between statin exposure and hepatotoxicity is less clearly defined.[8] A better understanding of the potential of statins to cause liver toxicity is critical for appropriately formulating benefit-risk decisions in the use of these agents.

Recently published studies of potential statin-induced hepatotoxicity in patients without underlying liver disease have been reassuring. Systematic reviews have concluded that elevated results of liver function tests (LFTs) among statin-treated patients are uncommon and similar to rates in non-statin-exposed patients.[9,10] Although several cases of hepatic failure linked to lovastatin have been reported, serious liver toxicity also appears to be rare.[11-13] Recently, the National Lipid Association recommended against routine liver function monitoring for patients receiving statins.[14]

The risk of statin-induced hepatotoxicity among patients with pre-existing liver disease, however, is of particular concern in that these patients may be particularly vulnerable to any possible adverse hepatic effects of statins.[15,16] Improved understanding of the magnitude of this risk is crucial: if there is a low risk of adverse hepatic outcomes with statin therapy, the cardioprotective benefits of statins may be inappropriately denied to this patient population because of an unwarranted fear of liver damage. Unfortunately, there are few data on statin-induced hepatotoxicity among patients with pre-existing liver disease, as they have generally been excluded from clinical trials.

In order to better understand the effects of statins on liver-related outcomes among patients with liver disease, we performed a retrospective cohort study of lovastatin use among members of a large integrated healthcare delivery system.

Methods

Study Subjects

Subjects were adult members of the Kaiser Permanente, Northern California (KPNC) Medical Care Program with at least 13 months of continuous health-plan membership between 1995 and mid-2004. KPNC is a large, integrated healthcare-delivery system in Northern California, USA, with 3.2 million members for whom extensive clinical information is available during periods of active membership. The study was approved by the Institutional Review Board of the Kaiser Foundation Research Institute.

Eligible patients had evidence of liver disease at baseline including at least two tests 6–18 months apart showing elevated ALT or AST levels, or who had a diagnosis of liver disease, such as chronic viral hepatitis, a metabolic disorder affecting the liver, or other chronic alcoholic or non-alcoholic liver disease (see table I). Diagnoses of viral hepatitis were

Table I. Liver disease inclusion criteria

Chronic hepatitis (without liver failure)
Viral hepatitis B without mention of hepatic coma (no hepatitis D)
Viral hepatitis B without mention of hepatic coma (with hepatitis D)
Viral hepatitis C without mention of hepatic coma
Other specified hepatitis without mention of hepatic coma
Metabolic disorders
Haemochromatosis
Wilson's disease
Other chronic liver diseases
Chronic liver disease and cirrhosis
Alcoholic fatty liver
Alcoholic cirrhosis of liver
Alcoholic liver damage, unspecified
Chronic hepatitis (excludes viral hepatitis)
Chronic hepatitis, unspecified
Chronic persistent hepatitis
Other chronic hepatitis
Cirrhosis of liver without mention of alcohol/NOS
Biliary cirrhosis
Other chronic nonalcoholic liver disease
Unspecified chronic liver disease without mention of alcohol
α_1 Antitrypsin deficiency

NOS = not otherwise specified.

validated by patients' serology tests. Patients were excluded if they had received a statin medication at any time in the year prior to their entry to the cohort, had evidence of drug-induced liver disease, a benign disorder of bilirubin excretion or had been diagnosed with cancer in the previous 5 years.

Predictor and Outcome Variables

The predictor variable was the receipt of lovastatin medication from a KPNC pharmacy, which served as a proxy for lovastatin exposure. For many years, lovastatin has been the statin most commonly prescribed at KPNC, accounting for 67% of all statin prescriptions. The percentage of other statins prescribed during this period were as follows: simvastatin, 27%; atorvastatin, 5%; pravastatin, 1%; rosuvastatin, <1%; and cerivastatin, <1%. Lovastatin exposure was defined dynamically so that an individual patient could contribute both exposed and unexposed time during the follow-up period. For the baseline analysis, an additional 30 days of exposure was added to a subject's last prescription to account for possible persistent hepatic effects of lovastatin.

The primary outcome variable, based on Hy's Rule, was defined as a concurrent serum ALT ≥3 × the upper limit of normal (ULN), a serum total bilirubin ≥2 × ULN, and a serum alkaline phosphatase <1.5 × ULN.[17] Hy's Rule was defined heuristically by Dr Hyman Zimmerman as a liver test profile that is associated with a particularly poor prognosis for patients with drug-induced liver disease;[17] recent validation studies support this assertion.[18-20]

Two secondary outcomes were also defined. 'Liver injury' was defined as an elevation of serum ALT and was categorized as either 'moderate' (an ALT elevation 3–10 × ULN) or 'severe' (an ALT elevation >10 × ULN). If the ALT was elevated at the time of the patient's entry to the cohort, the baseline value was substituted for the ULN. 'Cirrhosis/liver failure' was defined as the occurrence of a new diagnosis of cirrhosis or a diagnosis that indicated impaired hepatic synthetic function, elevated portal pressures or liver failure (including ascites, oesophageal varices, fulminant liver failure or liver transplant). The major ('combined') secondary outcome was defined as the first occurrence of any of the individual secondary outcomes.

Methods of Analysis

Subjects were followed forward in time and were censored at the first occurrence of any of the following events: death, health plan disenrollment, an outcome event 30 days after a patient's last lovastatin prescription or prescription of a statin other than lovastatin. For the analysis of each endpoint, subjects were excluded if they had evidence of that endpoint at baseline.

The incidence rate was calculated as the ratio of the number of outcome events divided by the number of person-days at risk.[21] The primary univariate measure of association was the incidence rate ratio (IRR) defined as the incidence rate of the lovastatin-exposed time periods divided by the incidence rate of the lovastatin-unexposed time periods.[21] Ninety-five percent CIs for the IRRs were calculated by an exact algorithm.[22]

Multivariate analyses were conducted using extended Cox models, including time-varying covariates that allowed for appropriate attribution of lovastatin-exposed and unexposed follow-up time.[23] Covariates included in these models included gender and age at entry into the cohort (age was entered as a four-level categorical variable which fits the data significantly better than when entered as a continuous variable). The cirrhosis/liver failure endpoint was also adjusted for baseline ALT level (entered as a categorical variable); laboratory-based endpoints could not be similarly adjusted as this variable was also the outcome in these analyses.

Analyses of the major secondary outcomes were examined across subgroups defined hierarchically by their entry diagnoses. These stratification categories were viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), other diagnoses and those subjects who entered the cohort on the basis of abnormal LFT values only.

Ancillary Analyses

Five ancillary analyses were defined *a priori*. In the baseline analysis, we allowed for theoretical

toxicity of lovastatin to persist for 30 days following the last lovastatin exposure; if such toxic effects persisted beyond 30 days, these analyses would underestimate the adverse effects of lovastatin. To test this assumption, we repeated the baseline analysis, assuming that any potential toxicity of lovastatin persisted indefinitely; this analysis amounted to a comparison of 'ever-lovastatin exposed' patients to 'never-lovastatin exposed' patients. Under this assumption, any adverse hepatic outcome in a patient who was currently taking or had previously taken lovastatin at any time would be attributed to the lovastatin. Control subjects in this analysis, by definition, were never prescribed lovastatin during the follow-up period.

The relationship between cumulative lovastatin exposure and the secondary outcomes was analysed by estimating the risk of each outcome in subgroups defined by quartiles of total lovastatin exposure (by cumulative amount or total days of exposure). Each of these risks was compared with that in the lovastatin-unexposed reference group and a test for trend applied, using orthogonal polynomial contrasts on the coefficients of categorical levels of the exposure variable.[24]

The interaction between exposure to lovastatin and other medications on the risk of the major secondary outcome was examined in extended Cox models, using time-varying covariates and appropriate interaction terms.[23] The potentially interacting medications tested were the fibric acid-derivatives and cytochrome P450 (CYP) 3A4 inhibitors, which can cause elevated serum lovastatin levels.[25] The specific drugs included in these analyses were gemfibrozil, fenofibrate, itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, nefazodone and all human immunodeficiency virus protease inhibitors.

Channelling bias (confounding by contraindication) could pose a serious threat to validity if clinicians avoided the use of statins in those patients with greater evidence of liver disease.[26] To examine this possibility, a new cohort was assembled of patients with low-density lipoprotein (LDL)-cholesterol levels ≥160 mg/dL and divided into three hierarchical groups based on the strength of evidence for liver disease. Group 1 had both a liver-disease diagnosis and at least two elevated LFT values within an 18-month period, group 2 had either a liver disease diagnosis or elevated LFT values, but not both (groups 2a and 2b, respectively) and group 3 had no evidence of liver disease or LFT elevation. Rates of lovastatin prescription were then calculated separately for each group.

Another source of potential bias could be the tendency of clinicians to more frequently perform liver function testing on patients taking lovastatin, increasing the likelihood of finding abnormal values (surveillance or detection bias).[21] To test this possibility, rates of liver function testing were compared between lovastatin-exposed and unexposed periods, using Poisson regression models with generalized estimating equations.[27]

Results

Overall, 93 106 KPNC patients met the eligibility criteria, of whom approximately 14.5% had received at least one lovastatin prescription (table II). Lovastatin-treated patients were older and more likely to be male, consistent with the demographics of patients at higher risk for coronary heart disease. The median length of lovastatin exposure was 9 months, consistent with the high rates of nonadherence in other studies of statins.[28-30] Compared with patients who received at least one lovastatin prescription, those who were never exposed to lovastatin were more likely to have baseline ALT level elevations that were moderate (6.6% vs 9.6%, respectively) or severe (1.2% vs 2.3%, respectively).

Overall, we found no evidence that, on average, exposure to lovastatin was associated with adverse hepatic outcomes (table III). In fact, lovastatin exposure was associated with a substantial and statistically significant decrease in the risk of all outcomes studied.

For example, in the univariate analysis, exposure to lovastatin was associated with a 72% decrease in the risk of developing a primary-outcome event (IRR 0.28, 95% CI 0.12, 0.55); this association was not attenuated by adjustment for age and sex.

Table II. Patient characteristics[a]

Characteristic	All patients	Ever lovastatin exposed	Never lovastatin exposed	p-Value
Number [n (%)]	93 106	13 491 (14.5)	79 615 (85.5)	
Mean age in years (SD)	48.4 (13.5)	53.9 (11.4)	47.5 (13.6)	<0.0001
Men [n (%)]	56 900 (61.1)	8 394 (62.2)	48 506 (60.9)	0.004
Median length of follow-up time [mo (IQR)]	28.8 (12.1–58.2)	35.0 (16.0–62.0)	27.9 (11.5–57.4)	<0.0001
Median length of lovastatin exposure [mo (IQR)]		9.1 (4.3–19.1)		
Baseline ALT [n (%)]				<0.0001
no baseline ALT	20 394 (21.9)	2 465 (18.3)	17 929 (22.5)	
0.1–1.4 × ULN	37 873 (40.7)	6 209 (46.0)	31 664 (39.8)	
1.5–3.0 × ULN	24 341 (26.1)	3 762 (27.9)	20 579 (25.9)	
3.1–10.0 × ULN ('moderate')	8 508 (9.1)	891 (6.6)	7 617 (9.6)	
>10.0 × ULN ('severe')	1 990 (2.1)	164 (1.2)	1 826 (2.3)	
Reason for entry into cohort [n (%)]				
viral hepatitis	26 029 (28.0)	1 454 (10.8)	24 575 (30.9)	<0.0001
ALD	4 282 (4.6)	347 (2.6)	3 935 (4.9)	
NAFLD	1 497 (1.6)	275 (2.0)	1 222 (1.5)	
other diagnosis	16 097 (17.3)	2 145 (15.9)	13 952 (17.5)	
abnormal LFTs	45 201 (48.6)	9 270 (68.7)	35 931 (45.1)	

a ALT values are presented as the number of times the ULN, since assays (and their normal ranges) changed over the course of the study period. Some patients admitted to the cohort for a liver-disease diagnosis did not have an ALT prior to cohort entry.

ALD = alcoholic liver disease; **IQR** = interquartile range; **LFT** = liver function test; **NAFLD** = non-alcoholic fatty liver disease; **ULN** = upper limit of normal.

Among those patients exposed to lovastatin, the absolute risk of developing a primary-outcome endpoint in this cohort was very low, with an incidence rate of 62 events per 100 000 person-years (95% CI 19, 105); among the unexposed group, the rate was 224 events per 100 000 person-years (95% CI 206, 242).

Similarly, lovastatin exposure was associated with a large and statistically significant decrease in the risk of any secondary outcome (IRR = 0.48, 95% CI 0.42, 0.55). The decrease in risk was slightly attenuated in the multivariate extended Cox model (IRR = 0.54, 95% CI 0.47, 0.62). Lovastatin-exposed patients were less likely to develop ALT elevations that were considered moderate (IRR =

Table III. Results of baseline analysis[a]

Outcome	Exposed to lovastatin		Unexposed to lovastatin		Univariate person-days	Multivariate ECM
	events	person-days	events	person-days	analysis [IRR (95% CI)]	[HR[b] (95% CI)]
Primary outcome	8	4 720 423	616	100 465 184	0.28 (0.12, 0.55)	0.28 (0.14, 0.57)
Combined secondary outcome	201	3 823 746	7751	71 100 756	0.48 (0.42, 0.55)	0.54 (0.47, 0.62)
Individual secondary outcomes						
liver injury, moderate	168	3 967 277	5796	76 080 540	0.56 (0.47, 0.65)	0.69 (0.59, 0.81)
liver injury, severe	17	4 162 824	660	81 438 120	0.50 (0.29, 0.81)	0.64 (0.40, 1.04)
cirrhosis/liver failure	50	4 586 889	3581	93 829 395	0.29 (0.21, 0.38)	0.28 (0.21, 0.37)

a Principal univariate (person-days) and multivariate (extended Cox model) results for primary and secondary outcomes under the assumption that any hepatotoxic effects of lovastatin persist for 30 days after the last lovastatin prescription. Incidence rate ratios refer to rates for lovastatin-exposed person-days compared with non-lovastatin exposed person-days.

b Adjusted for age and sex (and baseline ALT level for the cirrhosis/liver failure outcome).

ECM = extended Cox model; **HR** = hazard ratio; **IRR** = incidence rate ratio.

Table IV. Results of 'ever-exposed' versus 'never-exposed' analysis[a]

Outcome	Ever exposed to lovastatin		Never exposed to lovastatin		Univariate person-days	Multivariate ECM
	events	person-days	events	person-days	analysis [IRR (95% CI)]	[HR[b] (95% CI)]
Primary outcome	16	6 439 227	615	99 748 986	0.40 (0.24, 0.66)	0.42 (0.25,0.69)
Combined secondary outcome	292	5 125 832	7727	70 429 681	0.52 (0.46, 0.58)	0.58 (0.51, 0.65)
Individual secondary outcomes						
liver injury, moderate	241	5 336 866	5770	75 471 611	0.59 (0.52, 0.67)	0.73 (0.64, 0.83)
liver injury, severe	31	5 655 450	655	80 784 080	0.68 (0.45, 0.97)	0.87 (0.60, 1.25)
cirrhosis/liver failure	90	6 242 423	3569	93 101 474	0.38 (0.30, 0.46)	0.36 (0.29, 0.44)

a Principal univariate (person-days) and multivariate (ECM) results for primary and secondary outcomes under the assumption that any hepatotoxic effects of lovastatin persist indefinitely. IRRs refer to rates of lovastatin-exposed person-time compared with non-lovastatin exposed person-time.

b Adjusted for age and sex (and baseline ALT level for the cirrhosis/liver failure outcome).

ECM = extended Cox model; **HR** = hazard ratio; **IRR** = incidence rate ratio.

0.56, 95% CI 0.47, 0.65) or severe (IRR = 0.5, 95% CI 0.29, 0.81) and were less likely to receive a diagnosis of cirrhosis or liver failure (IRR = 0.29, 95% CI 0.21, 0.38) than unexposed patients. Some attenuation was noted in the multivariate analyses, particularly in the liver-injury outcomes (table III). Of note, adding baseline ALT adjustment to the multivariate models did not result in substantial changes in the estimates of the effect of lovastatin on adverse hepatic outcomes. The absolute risk for developing a secondary outcome among the lovastatin-exposed patients was 1920 events per 100 000 person-years (95% CI 1655, 2185 events); the corresponding rate in the unexposed group was 3982 events per 100 000 person-years (95% CI 3893, 4070 events).

To test the sensitivity of these analyses to the assumption that hepatic effects of lovastatin persist for only 30 days following discontinuation of the drug, we repeated the major analyses making the assumption that the effect of any lovastatin exposure persisted indefinitely (table IV). This assumption caused an expected increase in the IRR for the primary outcome from 0.28 to 0.40, which remained statistically significant (95% CI 0.24, 0.66). The IRR for the combined secondary outcome attenuated slightly from 0.48 to 0.52 (95% CI 0.46, 0.58). As expected, the hazard ratios for each of the individual secondary outcomes all increased toward the null but remained statistically significant with the exception of the multivariate severe liver-injury outcome which was similar to the baseline analysis.

The association between lovastatin exposure and a reduced incidence of any secondary outcome was generally consistent across all categories of liver-disease diagnoses that resulted in patients' admission to the analytical cohort (table V). All of these associations were significant with the exception of NAFLD, which was likely due to the very small numbers of clinically confirmed cases in the exposed group (n = 3). Stratified analyses were not carried out for the primary outcome because of the very small numbers of cases in the exposed group (n = 8).

There was evidence of a relationship between total cumulative lovastatin exposure and the combined secondary outcome; this was true whether 'exposure' was defined as the cumulative amount of lovastatin prescribed ($p < 0.0001$, figure 1) or total days of exposure (data not shown). This relationship was also present for the laboratory endpoints, but not for the disease-defined endpoints, although these subgroup analyses were limited by small numbers of outcome events in these subgroups. We also found no evidence that concomitant use of other medications modified the association between lovastatin exposure and the hepatic outcomes tested (p-value for interaction = 0.14).

At baseline, moderate and severe ALT elevations were less common in the lovastatin-exposed group (table II), although the absolute differences between groups were small. In a separate analysis, we found no strong evidence for channelling bias: rates of lovastatin prescription were comparable across

Table V. Stratified analyses of secondary outcomes[a]

Outcome	Exposed to lovastatin		Unexposed to lovastatin		Univariate person-days	Multivariate ECM
	events	person-days	events	person-days	analysis [IRR (95% CI)]	[HR[b] (95% CI)]
Secondary outcomes (overall)	201	3 823 746	7751	71 100 756	0.48 (0.42, 0.55)	0.54 (0.47,0.62)
Baseline diagnosis						
viral hepatitis	36	361 229	3448	24 123 605	0.70 (0.49, 0.97)	0.71 (0.51,0.99)
ALD	15	78 538	821	1 843 693	0.43 (0.24, 0.71)	0.38 (0.23,0.65)
NAFLD	3	65 758	77	890 358	0.53 (0.11, 1.62)	0.59 (0.18,1.90)
other diagnosis	28	517 676	1200	11 602 712	0.52 (0.34, 0.80)	0.54 (0.37, 0.80)
abnormal LFTs	119	2 800 545	2205	32 640 389	0.63 (0.52, 0.76)	0.76 (0.63,0.92)

a Univariate and multivariate analyses stratified by baseline entry diagnosis (see text for methodology). 'Secondary outcomes (overall)' refers to crude, non-stratified results for comparison to stratified analysis.

b Adjusted for age and sex.

ALD = alcoholic liver disease; **ECM** = extended Cox model; **HR** = hazard ratio; **IRR** = incidence rate ratio; **LFTs** = liver function tests; **NAFLD** = non-alcoholic fatty liver disease.

groups defined by increasing likelihood of liver disease, ranging from 31% to 44%, and the differences were not monotonically related to the ordered categories of liver disease (table VI). Analysis of liver function testing patterns showed that rates of testing were 46% higher during periods of lovastatin exposure than during periods of non-exposure (IRR = 1.46, 95% CI 1.43, 1.49).

Discussion

Contrary to concern regarding the potential hepatotoxicity of statins among patients with baseline liver disease, these data suggest that exposure to lovastatin was not associated with an increased risk of adverse hepatic outcomes. In fact, we found a lower risk of adverse hepatic outcomes in patients treated with lovastatin. These findings generally persisted after multivariate adjustment, were consistent across several different liver-disease endpoints and were insensitive to changes in several analytical assumptions.

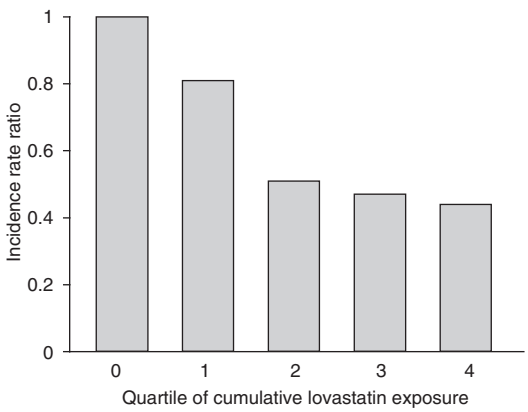

Fig. 1. Relationship between quartile of cumulative lovastatin exposure and the combined secondary outcome ($p < 0.0001$, test for trend). '0' refers to the no lovastatin exposure (reference) group; 1–4 refer to quartiles of total cumulative dose of lovastatin exposure, with 1 being the lowest exposure quartile and 4 being the highest exposure quartile.

Several aspects of this study lend strength to the observed results. We employed a retrospective cohort study design that preserved the temporal relationship between exposure and outcomes, and we found some evidence for a relationship between the cumulative lovastatin exposure and the risk of secondary outcomes (though this association was not consistent for all endpoints). The effects were present across a range of different outcomes and were generally consistent among different classes of baseline liver-disease diagnoses. In addition, there appeared to be no statistically significant interaction with other concomitant medications.

These results are consistent with other recently published data from smaller cohorts. Chalasani et al.,[31] observed that patients with elevated LFTs who were prescribed a statin did not have significantly higher rates of enzyme elevations than patients who were not exposed to a statin. Vuppalanchi et al.,[32] reported similar results in a study examining exposure to lovastatin specifically. One small study of pravastatin, as yet reported only in abstract

Table VI. Analysis of potential channelling bias[a]

Group	Liver-disease category	Lovastatin use after ID		
		≥1 prescription	no prescription	% use
1	Liver disease diagnosis and ≥2 LFT elevations	1 441	2 343	38
2a	Liver disease diagnosis only	1 519	3 325	31
2b	≥2 LFT elevations only	8 351	10 392	44
3	No liver disease diagnosis or LFT elevation	102 652	147 965	41

a Rates of lovastatin prescription by level of liver disease among patients with low-density lipoprotein-cholesterol ≥160 mg/dL. '% use' refers to cumulative incidence of receiving a lovastatin prescription at any time during follow-up period.

ID = index date (the date on which the patient developed the condition that led them to be placed in this category); **LFT** = liver function test.

form, also found no evidence of statin hepatotoxicity among patients with pre-existing liver disease.[33]

The concept that lovastatin might be beneficial for patients with liver disease was unexpected but is consistent with newly emerging data suggesting that the pleiotropic effects of statins might favourably affect the course of chronic hepatic disease, especially NAFLD (a common condition in patients with elevated lipid levels).[8,34] To date, three treatment case series have described the effects of statin therapy given to a combined total of 37 patients with documented NAFLD; in all studies, patients showed improvement in a variety of outcome variables including liver function tests, radiographic imaging and biopsies.[35-37]

Because of the retrospective observational nature of this study, threats to internal validity must be considered carefully. Most important is the potential for channelling bias: the possibility that clinicians may have avoided prescribing lovastatin for patients with more evidence of liver disease. We did find that patients with more severe elevations of liver enzymes were less likely to be prescribed lovastatin, although the absolute magnitude of these differences were small and are unlikely to be sufficient to account for the large between-group differences observed. In addition, the analyses of clinical-diagnosis outcomes included adjustment for baseline ALT. We also found that the rates of lovastatin prescription were fairly similar across categories defined by increasing evidence of hepatic disease. However, this analysis may not be sensitive to more subtle forms of channelling bias. Consistent with good clinical practice, we found that patients underwent liver function testing more frequently while they were taking lovastatin. Although this differential liver function testing is consistent with surveillance bias, in the context of these results, this difference is actually a conservative bias: even though lovastatin-exposed patients were tested more frequently, they experienced a lower incidence of laboratory-based adverse outcomes. We also found no evidence for an interaction between lovastatin and other drugs as an explanation for these findings. Importantly, we found that even under the most conservative assumption that any adverse hepatic outcome following any exposure to lovastatin was due to that exposure, there was no evidence of increased hepatic risk among patients who had ever been prescribed lovastatin.

Despite these efforts at identifying and controlling bias, several limitations of this study should be recognized. First, we used receipt of a lovastatin prescription as a proxy for ingestion of the medication; we have no information on actual patient adherence levels. However, the most likely form of non-adherence is failure to take the KPNC-provided medication (obtaining lovastatin from a non-KPNC pharmacy is unlikely); in this case, bias resulting from non-adherence is a conservative bias, causing misattribution of adverse hepatic outcomes to lovastatin when the patient was not actually taking the drug. We adjusted for age, gender and baseline ALT level, but did not have sufficient data to adjust for other potentially important confounders, such as alcohol use or adverse hepatic reactions to a medication or over-the-counter dietary supplement. Similarly, we cannot determine whether patients with liver disease who were prescribed a statin

might have received more aggressive concomitant therapies, such as weight loss regimens for patients with NAFLD. Despite the very large size of the database, the number of events for some outcomes (such as primary outcome and NAFLD) was too small to permit meaningful stratified or dose-response analyses. Any degree of severity of persistent LFT elevation was permitted for cohort entry, so that the study group contained a wide range of LFT elevations. Finally, like all observational studies, subtle biases and unmeasured confounding may always be present and these results require confirmation in other populations and with other study designs, although the consistency of these findings with those of other investigators is reassuring.

While we observed interesting reductions in hepatic risks among lovastatin-treated patients, these observations must be approached cautiously, given the retrospective and observational nature of these analyses. Our findings, and those of other investigators,[35-37] suggest that future studies of the potential hepatoprotective effects of statins may be appropriate; use of statins for this purpose, however, should occur only in the setting of carefully monitored clinical trials.

Conclusions

In summary, we found that, among patients with evidence of liver disease at baseline, exposure to lovastatin was not associated with an increased incidence of adverse hepatic outcomes and that the absolute risk of adverse hepatic outcomes was low. These data do not support recommendations for avoiding the use of statins in this patient population.

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Correspondence: Dr *Andrew L. Avins*, Kaiser Permanente Division of Research, 2000 Broadway, 3rd Floor, Oakland, CA 94612, USA.
E-mail: andrew.avins@ucsf.edu