

An Assessment of Statin Safety by Hepatologists

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The purpose of the Liver Expert Panel was to provide advice to the National Lipid Association's (NLA) Safety Task Force in response to specific questions concerning liver-associated risks of statin therapy. The panel was composed of academic hepatologists with clinical and research interests in nonalcoholic fatty liver disease, lipid metabolic disorders, and drug hepatotoxicity. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;97[suppl]:77C–81C)

Questions Posed by the National Lipid Association to the Liver Expert Panel

Are elevations in serum aminotransferase levels associated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, or statin, therapy?

- Response: Yes
- Confidence/level of evidence: 1A (Table 1)

RATIONALE. The Liver Expert Panel of the National Lipid Association (NLA) affirms that there is a relation between statin therapy and elevations in serum aminotransferase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]). This has been consistently demonstrated in clinical trials performed during statin phase 2 and 3 development programs and in long-term, end point trials.¹ The prescribing information for each statin cites these associations. Aminotransferase elevations >3 times the upper limit of normal generally occur in <1% of patients across the dose range for marketed statins; the exceptions are aminotransferase elevations of this magnitude that occur in 2%–3% of patients receiving atorvastatin 80 mg/day or the combination of ezetimibe and a statin.^{2–4}

Although the relation between statin therapy and aminotransferase elevations appears to be clear-cut, it is difficult to conclude with certainty that statins are causally related to these elevations or to be precise about the exact incidence. Considerable spontaneous fluctuations in aminotransferase levels occur over time in a population. In multiple studies, the incidence of aminotransferase elevations was similar in patients treated with statin or placebo patients. Moreover, nearly 50% of hyperlipidemic patients have coexisting non-

alcoholic fatty liver disease (NAFLD), and it is well known that aminotransferase levels fluctuate in NAFLD.⁵

Are statin-associated elevations in aminotransferase levels indicative of liver damage or dysfunction?

- Response: No
- Confidence/level of evidence: 2C

RATIONALE. Isolated elevations of aminotransferases in the absence of increased bilirubin levels have not been linked clinically or histologically with evidence of acute or chronic liver injury.^{6–8} Other mechanisms have been proposed that could explain commonly observed aminotransferase elevations in individuals treated with statins, including a transient pharmacologic effect secondary to cholesterol reduction in hepatocytes, comorbid conditions such as diabetes mellitus and obesity, and the consumption of alcohol or nonstatin medications.⁶

Are statin-associated elevations in aminotransferases a class effect?

- Response: Yes
- Confidence/level of evidence: 1A

RATIONALE. The Liver Expert Panel affirms that elevations in aminotransferase levels have been reported with all doses of all marketed statins and that no particular statin appears to cause these elevations more frequently than others. This observation is supported by the official product labeling for each marketed statin^{2,3,9–13} and by long-term randomized end point trials.¹ A recent meta-analysis of 13 of these clinical trials, involving 49,275 patients, supports this assertion.¹⁴ Whereas fluvastatin demonstrated statistically significant higher aminotransferase elevations at certain doses in this meta-analysis, the Panel was not persuaded that this difference is clinically significant.

Does statin therapy increase the incidence of liver failure, liver transplants or death associated with liver failure in the general population?

- Response: Yes
- Confidence/level of evidence: 2D

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Table 1
Scales for assigning confidence and type of evidence* codes to the answers given to task force questions

Scale	Description
Confidence	
1	Very confident
2	Confident
3	Marginally confident
4	Not confident
Type of evidence	
A	<ul style="list-style-type: none"> Well-designed RCTs, including RCTs conducted in patients who reported adverse experiences
B	<ul style="list-style-type: none"> Single RCT with a highly statistically significant result Well-conducted retrospective case-control studies with adverse experiences as primary end points Managed care claims database analysis with a highly statistically significant result
C	<ul style="list-style-type: none"> Reports to regulatory agencies judged to exceed population averages and reporting bias Multiple case studies with nonblinded dechallenge and rechallenge Strong trends, not reaching statistical significance, for safety issues in large RCTs Well-conducted prospective cohort study giving a result that is statistically well above population average Metabolic or clinically surrogate studies
D	<ul style="list-style-type: none"> Undocumented opinion of experienced research investigators and clinicians Poorly controlled or uncontrolled studies Nondefinitive evidence from regulatory agency reporting systems or managed care claims databases
U	<ul style="list-style-type: none"> Unknown, no appropriate evidence, or evidence considered subject to bias

RCT = randomized controlled clinical trial.

*Support for evidence for or against contention that a potential human adverse experience is related to use of statins.

RATIONALE. Very rare case reports of liver failure have occurred in patients receiving statin therapy.^{1,15} Because the association between statin therapy and liver failure is rare, it is impossible to directly attribute liver failure to statin usage. Nevertheless, it is possible that these cases do represent an idiosyncratic reaction to the statin.

Significant liver damage appears to be extremely uncommon with statins, especially when one considers the magnitude of their use worldwide. Based on 232 cases of acute liver injury potentially associated with lovastatin reported to Merck's Worldwide Adverse Event Database (WAES), it was estimated that risk of liver failure attributable to lovastatin was 2 in 1 million patients.¹⁶ In an article in this supplement, Law and Rudnicka¹⁷ estimate that the incidence of statin-associated liver failure is about 1 per million person-years of use. Of the 51,741 patients who underwent liver transplantation in the United States between 1990 and 2002, there were 3 patients in whom the procedure was performed for acute liver failure presumably caused by statins.¹⁵ Of these 3 patients, 2 had acute liver failure while receiving cerivastatin and 1 had liver failure that was ap-

parently associated with simvastatin. After an extensive review of the literature, the Liver Expert Panel could find no direct evidence of death due to liver failure caused by statin therapy.

The mechanism that underlies the rare association of acute liver failure and statin therapy is not clear. Statins have been reported to unmask autoimmune type liver pathology in genetically predisposed individuals,^{18,19} but this appears to be very rare. Furthermore, the rare occurrence of liver failure due to an idiosyncratic reaction is not specific to statins and has been reported with a number of other commonly used medications (eg, isoniazid, nitrofurantoin).²⁰

In this Panel's opinion, the evidence presented indicates that liver failure may occur very rarely with statin therapy. Reports have described liver failure requiring transplantation, but not deaths due to liver failure. Reports from spontaneous reporting systems and other sources also suggest that the risk of liver failure is present with any statin, but the risk is quite remote.

Should liver enzymes and liver function tests be monitored in patients receiving long-term statin therapy?

- Response: No
- Confidence/level of evidence: 2B

RATIONALE. The Liver Expert Panel does not believe that the available scientific evidence supports the routine monitoring of liver biochemistries in asymptomatic patients receiving statins.^{1,6-8,15,16,21} The Panel makes this recommendation because (1) irreversible liver damage resulting from statins is exceptionally rare and is likely idiosyncratic in nature, and (2) no data exist to show that routine monitoring of liver biochemistries is effective in identifying the very rare individual who may develop significant liver injury from ongoing statin therapy. In the view of the Panel, routine monitoring will instead identify patients with isolated increased aminotransferase levels, which could motivate physicians to alter or discontinue statin therapy, thereby placing patients at increased risk for cardiovascular events (see "Recommendations to Healthcare Professionals" below).

Whereas it is not fruitful to measure aminotransferase levels in order to detect an adverse reaction to statin therapy, it may be prudent to obtain these tests during routine medical evaluations of patients. In this setting, if a patient receiving a statin is found to have an elevated aminotransferase, it is essential for the physician to exclude other etiologies such as viral hepatitis, alcohol consumption, or other medication-related causes (eg, use of nonsteroidal anti-inflammatory drugs).

Are any of the following conditions a contraindication for statin therapy?

- Chronic liver disease
- Response: No
- Confidence/level of evidence: 2B

- Compensated cirrhosis
 - Response: No
 - Confidence/level of evidence: 3D
- Decompensated cirrhosis or acute liver failure
 - Response: Yes
 - Confidence/level of evidence: 2D

RATIONALE. The Liver Expert Panel believes that neither chronic liver disease nor compensated cirrhosis should be considered a contraindication for statin therapy. This position is supported by studies demonstrating that the frequency and degree of aminotransferase elevations were the same in patients with 1 of these conditions, regardless of whether they received statin therapy.^{1,6}

Compensated cirrhosis is considered to be present when individuals have histologic or clinical evidence of cirrhosis but their liver function is preserved. The prevalence of compensated cirrhosis in adults in the United States is estimated to be <1%.²² The Liver Expert Panel did not identify any scientific evidence to support consideration of compensated cirrhosis as a contraindication for statin usage. Several studies have shown that the pharmacokinetics of various statins are not significantly altered in patients with Child's class A cirrhosis.^{2,3,10–13} Because patients with compensated cirrhosis may have normal aminotransferase levels, it is the opinion of the Liver Expert Panel that a substantial number of individuals with unsuspected but compensated cirrhosis have already taken statins over the years without excessive toxicity.

The Liver Expert Panel believes that decompensated cirrhosis (ie, cirrhosis associated with impaired liver function) or acute liver failure should remain a contraindication for statin therapy. However, it is not likely that statin therapy would be indicated in either of these conditions because lipid-lowering therapy would not likely be considered a relevant option in patients with such a life-threatening illness.²¹

Can statins be used in patients with NAFLD or non-alcoholic steatohepatitis (NASH)?

- Response: Yes
- Confidence/level of evidence: 1B

RATIONALE. The Liver Expert Panel believes that statins can be used safely in patients with either NAFLD or NASH. Moreover, individuals with NAFLD or NASH should be considered important targets for statin therapy because of their significantly increased cardiovascular risk. There is a high prevalence of suspected or unsuspected NAFLD in patients with hyperlipidemia, and it is not uncommon that aminotransferase levels are normal in patients with NAFLD.²³ Therefore, it is this Panel's opinion that a large number of hyperlipidemic patients with unsuspected NAFLD have already been treated with statins over the years without significant toxicity. Recent case-control studies have shown that individuals with elevated baseline liver enzymes and presumed NAFLD are not at higher risk for statin hepatotoxicity than are those with normal baseline

liver enzymes.^{7,8} Furthermore, small studies have shown that statins may actually improve liver histology in patients with NASH.^{24–26}

Recommendations of the Liver Expert Panel

Recommendations to regulatory authorities: Because there is no evidence that a relation exists between elevated serum aminotransferase levels and significant liver injury, or that routine monitoring of liver biochemistries will identify individuals likely to develop rare cases of idiosyncratic liver failure, the requirement for routine liver biochemistry monitoring in patients receiving any of the currently marketed statin therapies should be reexamined.^{1,6–8,15,16,21,27} The Liver Expert Panel is concerned that isolated elevations in aminotransferases may prompt health professionals to discontinue statin therapy inappropriately in patients otherwise at increased risk for an adverse cardiovascular event. The Panel is also concerned that patients may be unduly alarmed by the perceived implications of monitoring and may choose to discontinue or refuse statin therapy. Finally, preliminary estimates suggest that the costs associated with monitoring are very high.⁶

Recommendations to healthcare professionals: PATIENT MONITORING. Before instituting any type of medical therapy, it is advisable for the clinician to perform a complete and systematic history, physical examination, and pertinent laboratory testing. If, in the course of this workup, elevated aminotransferase levels are identified, they should be investigated in an appropriate fashion. Patients with chronically abnormal liver biochemical tests should undergo a thorough medical evaluation, and, if indicated, be referred to a gastroenterologist or hepatologist.

Outside of measuring liver biochemistries for the purpose of periodically updating a patient's medical history, we can find no scientific or medical basis for monitoring aminotransferase levels during long-term statin therapy as a measure to enhance patient safety. We acknowledge that the Panel's recommendations are at odds with current prescribing information for marketed statins; however, we are optimistic that the regulatory agencies and pharmaceutical industry will update their recommendations to be consistent with evidence-based data cited in this article.

EVALUATION OF A POTENTIAL ADVERSE EVENT. When a healthcare professional is concerned about the possible occurrence of a hepatotoxic reaction due to statin therapy (eg, because the patient reports jaundice, malaise, fatigue, lethargy, or related symptoms during treatment), the Liver Expert Panel believes that an assessment of fractionated bilirubin level is advisable. In the absence of biliary obstruction, bilirubin is a more reliable prognosticator of liver injury in the setting of drug toxicity.^{27,28} If the direct fraction of bilirubin is found to be increased in association with elevated aminotransferases, it is reasonable to assume that there is ongoing liver injury and further appropriate testing should be undertaken to ascertain the etiology.

WHEN TO REDUCE A STATIN DOSE OR DISCONTINUE THERAPY. There is no evidence that statin therapy should be altered or discontinued solely on the basis of elevated aminotransferase levels in an asymptomatic patient. Should more objective evidence of hepatic dysfunction be identified, such as hepatomegaly, clinical evidence of jaundice, elevated direct bilirubin level, or increased prothrombin time,^{20,29} statin therapy should be discontinued. The patient should be evaluated appropriately and referred to a gastroenterologist or hepatologist, if necessary.

NEW-ONSET LIVER DISEASE IN A PATIENT RECEIVING ONGOING STATIN THERAPY. Once a systematic and complete medical evaluation reveals significant liver disease in a patient receiving statin therapy, the etiology should be established. If a causal relation between significant liver injury and statin therapy cannot be excluded, then reinitiation of statin therapy is not recommended and alternative lipid-lowering strategies should be considered.

ANTICOAGULANT THERAPY AND ELEVATED AMINOTRANSFERASES DUE TO STATINS. There is no evidence that elevated aminotransferase levels due to statins affect response to anticoagulant therapy. Therefore, no modification in statin therapy is recommended.

STATIN THERAPY AND ALCOHOL CONSUMPTION. Mild-to-moderate alcohol consumption (ie, up to 1–2 drinks per day) is not a contraindication for statin therapy.²³

Recommendations to patients: The class of cholesterol-lowering medications called statins has the ability to lower the risk of a heart attack, stroke, and the need for hospital-based heart procedures by 25%–50%. Fortunately, the side effects associated with these drugs occur very infrequently. Side effects that affect the liver are rare. While taking statin medications, some blood tests traditionally obtained by physicians to monitor the liver may be elevated, but these test results do not indicate that the statin medication is causing serious liver problems. Serious liver damage due to statins is exceptionally rare. It is important to appreciate that a number of other commonly prescribed medications can cause similar reactions (eg, antibiotics, seizure medications).

Recommendations to researchers, funding agencies, and pharmaceutical companies: To promote and optimize appropriate use of statins in the dyslipidemic population, the Liver Expert Panel encourages research in the following areas:

- Pharmacogenomics of statin-associated aminotransferase elevations to clarify why some patients experience elevations and others do not
- Potential benefits of statin therapy in fatty liver disease, as demonstrated in preliminary studies^{24–26}
- Impact of statin therapy on the natural progression of cirrhosis and fibrosis

As indicated above, it is important that pharmaceutical manufacturers of statin products work with regulatory au-

thorities to modify recommendations for patient monitoring. In addition, pharmaceutical companies should carefully assess both the positive and negative effects that direct-to-consumer advertising has on the patient's understanding of statins.

Pharmaceutical companies are encouraged to release the results of clinical research performed with lipid-altering therapies as a part of the New Drug Application (NDA) for market approval. Future drug development should include a process for clinician-based peer-review of suspected hepatic events identified in clinical trials. This process would include but not be limited to the following:

- Communication with general practitioners regarding suspected hepatic adverse events and encouraging them to report adverse events (AEs) to the US Food and Drug Administration (FDA) via MedWatch (<http://www.fda.gov/medwatch/>)
- Education concerning AEs that would incorporate (1) procedures for systematic evaluation of an AE, (2) possible etiology of an AE, and (3) correct use of validated instruments in the assessment of causality

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