

# Final Conclusions and Recommendations of the National Lipid Association Statin Safety Assessment Task Force

James M. McKenney, PharmD,<sup>a,\*</sup> Michael H. Davidson, MD,<sup>b</sup> Terry A. Jacobson, MD,<sup>c</sup> and John R. Guyton, MD<sup>d</sup>

---

This article summarizes the final conclusions of the National Lipid Association (NLA) Statin Safety Task Force, based on a review and independent research of New Drug Application (NDA) information, US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) data, cohort and clinical trial results, and analysis of administrative claims database information and the assessment of its 4 Expert Panels, which focused on issues of statin safety with regard to liver, muscle, renal, and neurologic systems. Practical guidance in the form of recommendations to health professionals who manage the coronary artery disease risk of patients with statin therapy is provided. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006; 97[suppl]:89C–94C)

---

In the sections that follow, the National Lipid Association (NLA) Statin Safety Task Force draws from the extensive evidence so superbly presented and analyzed by the scientists and experts who authored the preceding articles in this supplement. The Task Force herein offers what it believes to be a summary of final conclusions that can be made based on this evidence and provides practical guidance in the form of recommendations to health professionals who manage the coronary artery disease risk of patients with statin therapy.

## The Liver and Statin Safety

**Final conclusions:** Asymptomatic elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) liver enzymes >3 times the upper limit of normal (ULN) are seen with all 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins.<sup>1</sup> According to data from New Drug Applications (NDAs) and the prescribing information for each marketed statin, elevations of this magnitude are seen in <1% of patients receiving initial and intermediate doses and in 2%–3% of patients receiving 80 mg/day.<sup>1</sup> It is evident that these elevations are related to the dose of the statin but not to the low-density lipoprotein (LDL) cholesterol reduction.<sup>2,3</sup> It is also evident that an elevation of

ALT and/or AST >3 times the ULN is most often transient and will resolve spontaneously in 70% of cases even if the statin and dose are continued unchanged.<sup>2,4</sup> To more accurately identify patients with a persistent liver test abnormality, some investigators have adopted a more rigorous definition, eg, ALT or AST >3 times the ULN on 2 consecutive occasions. When this definition is applied, the number of patients with a significant elevation drops from 300 per 100,000 person-years to 110 per 100,000 person-years.<sup>4</sup> Reduction in the dose or withdrawal of the statin regularly results in a return of the elevated enzyme levels to normal without adverse sequelae.

The cause of an elevation in liver transaminase levels during statin therapy has not been determined. Generally in clinical trials, the proportion of patients experiencing elevations is greater when individuals are given a statin than when they receive placebo, thus supporting the argument for a statin effect. However, confounding this is the fact that the population most likely to receive statin therapy is also the population most likely to experience liver function changes, including patients with diabetes mellitus or obesity, older individuals, and patients taking multiple medications.<sup>2</sup>

The most relevant question with regard to the liver and statin safety is not whether statins cause a significant increase in liver function test results, but whether they cause serious liver dysfunction or failure. The answer to this question is not clear, owing in part to the rarity of these events among statin users. A handful of case reports have been published that describe liver failure in patients receiving statin therapy, but a causal relation cannot be established from these data alone.<sup>1</sup> Data from the US Food and Drug Administration (FDA) Adverse Event

---

<sup>a</sup>National Clinical Research, Virginia Commonwealth University, Richmond, Virginia, USA; <sup>b</sup>Rush University Medical Center, Chicago, Illinois, USA; <sup>c</sup>Emory University, Atlanta, Georgia, USA; and <sup>d</sup>Duke University Medical Center, Durham, North Carolina, USA.

\*Address for reprints: James M. McKenney, PharmD, National Clinical Research, 2809 Emerywood Parkway, Suite 140, Richmond, Virginia 23294.

E-mail address: jmckenney@ncrinc.net.

Table 1  
Recommendations to healthcare professionals regarding the liver and statin safety<sup>1-5</sup>

1. During the routine general evaluation of patients being considered for statin and other lipid-lowering therapy, it is advisable to obtain liver transaminase levels. If these tests are found to be abnormal, further investigation should be performed to determine the etiology of the abnormal test results.
2. Until there is a change in the FDA-approved prescribing information for statins, it is appropriate to continue to measure transaminase levels before starting therapy, 12 weeks after initiating therapy, after a dose increase, and periodically thereafter. However, routine monitoring of liver function tests is not supported by the available evidence and the current recommendation for monitoring needs to be reconsidered by the FDA.
3. The clinician should be alert to patient reports of jaundice, malaise, fatigue, lethargy, and related symptoms in patients taking statin therapy as a signal of potential hepatotoxicity. Evidence for hepatotoxicity includes jaundice, hepatomegaly, increased indirect bilirubin level and elevated prothrombin time (rather than simple elevations in liver transaminase levels).
4. The preferred biochemical test to ascertain significant liver injury is fractionated bilirubin, which, in the absence of biliary obstruction, is a more accurate prognosticator of liver injury than isolated aminotransferase levels.
5. Should the clinician identify objective evidence of significant liver injury in a patient receiving a statin, the statin should be discontinued. The etiology should be sought and, if indicated, the patient referred to a gastroenterologist or hepatologist.
6. If an isolated asymptomatic transaminase level is found to be elevated 1-3 times the ULN, there is no need to discontinue the statin.
7. If an isolated asymptomatic transaminase level is found to be >3 times the ULN during a routine evaluation of a patient administering a statin, the test should be repeated and, if still elevated, other etiologies should be ruled out. Consideration should be given to continuing the statin, reducing its dose, or discontinuing it based on clinical judgment.
8. According to the Expert Liver Panel, patients with chronic liver disease, nonalcoholic fatty liver disease, or nonalcoholic steatohepatitis may safely receive statin therapy.<sup>1</sup>

FDA = US Food and Drug Administration; ULN = upper limit of normal.

Reporting System (AERS) database through 1999 included 30 cases of liver failure in individuals taking statins, for a reporting rate of 1 case per 1 million statin prescriptions.<sup>4</sup> The Merck Worldwide Adverse Event Database (WAES) included 22 cases of liver failure in patients taking lovastatin, for a rate of 1 case per 1.14 million patients.<sup>1</sup> Only 1 of the 51,741 patients who underwent liver transplantation between 1990 and 2002 was taking a marketed statin.<sup>1</sup> These data do not establish causality. In fact, because the rate of liver failure in a population not receiving statin therapy is about the same, it may support a conclusion that there is no relation between liver failure and statin therapy. Alternatively, cases of liver failure may represent idiosyncratic reactions that occur very rarely in patients taking statin therapy. In either case, the routine monitoring of liver enzyme levels may not identify these patients.

Based on the evidence, one would have to monitor transaminase levels in 100,000 patients each year for an average of 3 years to detect 110 patients who have consecutive elevations in ALT in order to identify the statistical 0.1 person who may experience liver failure, assuming that statins can cause liver failure in the first place.<sup>4</sup> Unfortunately, routine monitoring may lead to a temporary or permanent withdrawal of statin treatment, thus depriving a considerable number of patients of the life-protecting benefit of statin therapy.

Based on this, the NLA Statin Safety Assessment Task Force can find no evidence to support the continued monitoring of liver function tests in patients receiving statin therapy. However, because of medical-legal issues, we also believe that the cessation of liver function monitoring is not advisable until changes in the prescribing information for marketed statins occur. Thus, we recommend a thorough and timely review of these data by

regulatory authorities and the statin manufacturers and, if found warranted, removal of a recommendation for liver function monitoring from the prescribing information. Further, we believe that statin manufacturers who choose to market their statin directly to the consumer should not be required to include a caution regarding potential liver adverse effects as a part of a fair-balance statement. This only serves to confuse and unnecessarily alarm the public and potentially to discourage them from pursuing this life-sustaining therapy, an outcome that would not be in the public's best interest.

**Recommendations:** Table 1 presents our consensus recommendations to health professionals based on the evidence, interpretations, and assessments of liver issues and statin safety presented in this supplement.<sup>1-5</sup>

### The Muscle and Statin Safety

**Final conclusions:** Muscle symptoms (ie, pain, soreness, weakness, and/or cramps) or signs (creatinine kinase [CK] elevations) are arguably the most prevalent and important adverse effect associated with statin therapy. The occurrence of serious muscle toxicity with currently marketed statins fortunately is rare.<sup>6</sup> According to findings from 21 clinical trials providing 180,000 person-years of follow-up in patients treated with statin or placebo, myopathy (defined as muscle symptoms plus CK >10 times the ULN) occurs in 5 patients per 100,000 person-years and rhabdomyolysis in 1.6 patients per 100,000 person-years (placebo corrected).<sup>4</sup> This compares with the reporting rate of 0.3-2.2 cases of myopathy and 0.3-13.5 cases of rhabdomyolysis per million statin prescriptions from the FDA's AERS database<sup>7</sup> and with 1.6-3.5 cases of hospitalized myopathy (including

rhabdomyolysis) per 10,000 person-years from an analysis of an administrative managed care claims database.<sup>5</sup> (Note that these latter data have not been verified with chart review.) A CK level >10 times the ULN, or >2,000 U/L, was found in 23 patients per 100,000 person-years in clinical trials; this rate fell to zero when repeat measures were recorded.<sup>4</sup>

The most common muscle side effects remain myalgia (ie, muscle pain or soreness), weakness, and/or cramps without CK elevations.<sup>2,4,6</sup> These symptoms are most often tolerable, but occasionally can be intolerable and debilitating, requiring the statin to be withdrawn. Muscle symptoms have been reported in clinical trials to occur in 1.5%–3.0% of patients receiving statin therapy, most often without an elevation in the CK level, and at an equivalent rate in patients given placebo.<sup>2,4</sup> The incidence of muscle complaints among patients being treated in a practice setting ranges from 0.3%–33%.<sup>2</sup> The higher rate may occur partly because statin-intolerant patients and those with risk factors for muscle toxicity are more likely to be excluded from clinical trials.

Among marketed statins, it appears that the risk of drug-related muscle injury is roughly the same. All marketed statins cause the spectrum of muscle injury, but they are rarely severe, and very rarely progress to a life-threatening situation.<sup>2,4,6,7</sup> Fluvastatin and pravastatin, perhaps because they are the weakest inhibitors of HMG-CoA reductase, appear to cause the lowest frequency of rhabdomyolysis; simvastatin 80 mg (but not lower doses) appears to be associated with the highest frequency.<sup>2,4</sup> The use of more hydrophilic statins (ie, pravastatin and rosuvastatin) does not offer protection from muscle toxicity as symptoms of muscle damage and rhabdomyolysis have been reported with these statins.<sup>2</sup>

Cerivastatin was unique among the marketed statins in that it had unfavorable pharmacokinetic features, the potential for multiple drug interactions, and was marketed at a dose that exceeded its safety threshold. It caused a 5- to 7-fold greater incidence of muscle damage sequelae, including rhabdomyolysis and death.<sup>2,4</sup> Currently marketed statins do not have the unfavorable features of cerivastatin.

The exact mechanism for muscle injury from statin therapy is not known. However, it appears to be related to the blood concentration of the statin, which is influenced by the drug's pharmacokinetics and its potential for drug interactions, the statin dose, and the patient's myopathic risk factors (eg, age, renal disease, diabetes), but not by the LDL cholesterol level achieved. The latter is influenced mostly by the potency of HMG-CoA reductase inhibition in the hepatocyte.<sup>3</sup> Although muscle adverse effects can occur in patients taking the starting dose of a statin, symptoms are much more likely to occur with higher doses. Other situations that may raise the statin's blood levels include advanced age and frailty, small body frame, deteriorating renal function, infection, untreated hypothyroidism, interacting drugs—particularly with

statins metabolized by the cytochrome P450 system and gemfibrozil, perioperative periods, and alcohol abuse.<sup>2</sup> The theory that these toxicities are related to a reduction in muscle levels of ubiquinone has not been proved, and attempts to reduce muscle symptoms with coenzyme Q10 prophylaxis have given equivocal results and cannot be recommended.<sup>6</sup>

**Recommendations:** The NLA Task Force recommends that the generally accepted and widely used definition of myopathy be retained, namely, the presence of muscle pain, soreness, weakness, and/or cramps plus a CK level 10 times the ULN (see Table 2).<sup>6</sup> Presentation of muscle symptoms that cannot otherwise be explained in a statin-taking patient should prompt the measurement of a CK level. It is not necessary to monitor CK levels in patients receiving statin therapy. If the CK level is >10 times the ULN, a repeat measure is generally recommended to establish persistency. The Task Force is also aware that an occasional patient will describe intolerable muscle symptoms but not be found to have a CK level >10 times the ULN. In this case, the patient may be presumed to be experiencing myopathy for the purpose of further evaluation and workup.

The Task Force offers a new definition for rhabdomyolysis. This definition is an attempt to integrate differing definitions used by the FDA and clinical trialists. The definition is meant to identify the clinical situation where the risk of acute renal failure and urgent medical intervention is high. We chose a CK level of >10,000 U/L, in accord with the definition currently used by the FDA, regardless of whether the patient has experienced a change in renal function, because such a CK level places the patient at high risk of acute renal failure. A second component in our definition is a CK >10 times the ULN with worsening renal function and/or a requirement for medical intervention with intravenous hydration therapy. We acknowledge that CK levels may not always be >10 times the ULN in cases of diminishing renal function, especially if the laboratory sample is drawn some time after the event; thus, this should not be taken as an absolute criterion.

In Table 3, we present our consensus recommendations to health professionals based on the evidence, interpretations, and assessments of muscle issues and statin safety presented in this supplement.<sup>2-5</sup>

### The Kidney and Statin Safety Panel

**Final conclusions:** In the absence of rhabdomyolysis, acute renal failure or insufficiency does not appear to be caused by statin therapy.<sup>7</sup> Although case reports of renal failure have been reported in patients receiving statin therapy, they are encountered as frequently in patients receiving statins as in patients not receiving statins.<sup>2</sup> In the 3 pravastatin clinical trials (Cholesterol and Recurrent Events [CARE] trial, Long-Term Intervention with

Table 2  
New definitions to describe muscle findings in patients taking statins<sup>6</sup>

- Myopathy\*
  - Complaints of myalgia (muscle pain or soreness), weakness, and/or cramps, *plus*
  - Elevation in serum CK >10× the ULN
- Rhabdomyolysis
  - CK >10,000 IU/L, *or*
  - CK >10× the ULN plus an elevation in serum creatinine or medical intervention with IV hydration therapy<sup>†</sup>

CK = creatine kinase; IV = intravenous; ULN = upper limit of normal.

\*A patient may describe intolerable muscle symptoms but not be found to have a CK level >10 times the ULN. This patient may be considered to be experiencing myopathy for the purposes of further evaluation.

<sup>†</sup>The CK level may be <10 times the ULN depending on the temporal relation between the event and the drawing of the laboratory sample.

Table 3  
Recommendations to health professionals regarding the muscle and statin safety<sup>2-5</sup>

1. Whenever muscle symptoms or an increased CK level is encountered in a patient receiving statin therapy, health professionals should attempt to rule out other etiologies, because these are most likely to explain the findings. Other common etiologies include increased physical activity, trauma, falls, accidents, seizure, shaking chills, hypothyroidism, infections, carbon monoxide poisoning, polymyositis, dermatomyositis, alcohol abuse, and drug abuse (cocaine, amphetamines, heroin, or PCP).
2. Obtaining a pretreatment, baseline CK level may be considered in patients who are at high risk of experiencing a muscle toxicity (eg, older individuals or when combining a statin with an agent known to increase myotoxicity), but this is not routinely necessary in other patients.
3. It is not necessary to measure CK levels in asymptomatic patients during the course of statin therapy, because marked, clinically important CK elevations are rare and are usually related to physical exertion or other causes.
4. Patients receiving statin therapy should be counseled about the increased risk of muscle complaints, particularly if the initiation of vigorous, sustained endurance exercise or a surgical operation is being contemplated; they should be advised to report such muscle symptoms to a health professional.
5. CK measurements should be obtained in symptomatic patients to help gauge the severity of muscle damage and facilitate a decision of whether to continue therapy or alter doses.
6. In patients who develop intolerable muscle symptoms with or without a CK elevation and in whom other etiologies have been ruled out, the statin should be discontinued. Once asymptomatic, the same or different statin at the same or lower dose can be restarted to test the reproducibility of symptoms. Recurrence of symptoms with multiple statins and doses requires initiation of other lipid-altering therapy.
7. In patients who develop tolerable muscle complaints or are asymptomatic with a CK <10× the ULN, statin therapy may be continued at the same or reduced doses and symptoms may be used as the clinical guide to stop or continue therapy.
8. In patients who develop rhabdomyolysis (a CK >10,000 IU/L or a CK >10 times the ULN with an elevation in serum creatinine or requiring IV hydration therapy), statin therapy should be stopped. IV hydration therapy in a hospital setting should be instituted if indicated for patients experiencing rhabdomyolysis. Once recovered, the risk vs benefit of statin therapy should be carefully reconsidered.

CK = creatine kinase; IV = intravenous; PCP = phencyclidine; ULN = upper limit of normal.

Pravastatin in Ischaemic Disease [LIPID] study, and West of Scotland Coronary Prevention Study [WOSCOPS]), for example, renal failure and other renal diseases were reported more frequently in patients who were given placebo.<sup>4</sup> None of the other end point clinical trials with statins even report cases of renal disease.<sup>4</sup> In the FDA AERS database, the proportional reporting rate for renal failure is low, generally 0.3–0.9 cases per 1 million statin prescriptions.<sup>8</sup> In 2005 the FDA undertook the most comprehensive analysis of this topic to date, conducting a case-by-case review of 38 reports it had received of renal failure/insufficiency in patients receiving rosuvastatin.<sup>2</sup> The FDA reported that it could find no convincing evidence that statin therapy was associated with serious renal injury, concluding that “no consistent pattern of clinical presentation or of renal injury (ie, pathology) is evident among the cases of renal failure reported to date that clearly indicate causation by Crestor (rosuvastatin; AstraZeneca, Wilmington, DE) or other statins.”<sup>2</sup>

Although the evidence that statins cause renal failure is sparse, other evidence including small randomized controlled trials and post hoc analyses of large end point

trials suggest that statin therapy may slow the rate of decline in renal function. For example, post hoc analysis of the CARE and Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) trials of pravastatin and atorvastatin, respectively, report improved glomerular filtration rate (GFR) in patients treated with statin compared with controls.<sup>7</sup> Additionally, observation of >10,000 patients with and without diabetes receiving open-label rosuvastatin for up to 3.8 years revealed no progressive decline in renal function; instead there was an improvement in serum creatinine and GFR values.<sup>7</sup> These data suggest a potential renal-protective effect with statins. A number of large end point trials involving therapy with several different statins are under way in patients with compromised renal function, including dialysis patients; these should help clarify the role of statins in preserving renal function.

Proteinuria has been described only rarely with statins,<sup>3</sup> but recently it was found significantly more frequently in patients receiving rosuvastatin 80 mg than in patients given placebo.<sup>2,3,7</sup> In the same study, the frequency of proteinuria found with other doses of rosu-

Table 4  
Recommendations to health professionals regarding the kidney and statin safety<sup>2-4,7,8</sup>

1. During the management of patients with statin therapy, it is not necessary to carry out serum creatinine and proteinuria monitoring routinely for the purpose of identifying an adverse effect, although an assessment of renal function is advisable before initiating statin therapy.
2. If serum creatinine becomes elevated in a patient without rhabdomyolysis while receiving statin therapy, there is generally no need to withdraw the statin but in some cases, according to prescribing information, an adjustment in the statin dose may be required.
3. If unexpected proteinuria develops in a patient receiving a statin, there is no need to withdraw statin therapy or to alter the dose of the statin. An investigation into the cause of the proteinuria is warranted, as is consideration of a change in the statin dose as guided by the prescribing information for each statin.
4. Chronic kidney disease does not preclude the use of a statin. However, the dose of some statins should be adjusted in cases of moderate or severe renal insufficiency<sup>7</sup>

vastatin (5–40 mg) currently on the market, as well as with marketed doses of atorvastatin, pravastatin, and simvastatin, was no different than that found with placebo allocation.<sup>2,7</sup> This latter observation supported our Renal Expert Panel's answer of "no" when asked whether statins cause proteinuria in humans.<sup>7</sup> Part of the explanation for proteinuria is that individuals who are candidates for statin therapy often are prone to proteinuria owing to diabetes, hypertension, or advancing age. Further confounding the interpretation of these data is that the proteinuria found in clinical trials is often detected during random spot urine testing with a dipstick in patients participating in long-term, open-label studies that often lack a placebo comparison group.<sup>2</sup>

Other evaluations support the suggestion that the proteinuria observed with statin therapy is the result of physiologic interference with protein uptake in renal tubules.<sup>2,3</sup> In vitro studies using an opossum proximal tubular epithelial kidney cell line in culture demonstrated that all statins can interfere with protein renal tubular uptake through a concentration-dependent inhibition of HMG-CoA reductase.<sup>3</sup> Furthermore, when mevalonate is added to the culture, the inhibition of protein uptake was reversed, further validating that the mechanism of the statin's effect on protein uptake is dependent on HMG-CoA reductase inhibition.<sup>3</sup> Consistent with this proposed mechanism is the finding that low-molecular-weight protein of renal tubular origin is found in the urine of these patients.<sup>2,3</sup> These studies also illustrate that proteinuria is at least possible with all statins at some concentration, but is more likely to be seen with statins that are potent inhibitors of HMG-CoA reductase.<sup>2</sup> In their analysis of these data, the FDA concluded that proteinuria in patients receiving statins is not associated with renal impairment or renal failure.<sup>2</sup>

**Recommendations:** Table 4 includes our consensus recommendations to health professionals based on the evidence, interpretations, and assessments presented in this supplement regarding the kidney and statin safety.<sup>2-4,7,8</sup>

### Neurologic Disorders and Statin Safety

**Final conclusions:** The occurrence of peripheral neuropathy in patients taking a statin is very rare.<sup>9</sup> A causal relation is not supported by the Heart Protection Study

(HPS), a randomized, placebo-controlled clinical trial in >20,000 individuals in which peripheral neuropathy was recorded in 11 patients who received simvastatin and in 8 patients who received placebo.<sup>2</sup> Another large randomized, placebo-controlled trial in elderly patients, the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) study, reported no evidence of peripheral neuropathy with pravastatin therapy.<sup>2</sup> Case-control and cohort studies present conflicting findings, but, according to a meta-analysis of 4 cohort studies, an odds ratio of 1.8 (95% confidence interval, 1.1–3.0;  $p = 0.001$ ) was found, favoring the conclusion of a relation between statin use and peripheral neuropathy.<sup>4</sup> The association is also supported by 16 case reports of peripheral neuropathy in patients taking statins; symptoms of peripheral neuropathy generally appeared within 2 months of the initiation of statin therapy and dissipated after withdrawal of the statin.<sup>4</sup> In 1 case report, 4 different statins were started and stopped in succession with the concurrent appearance and disappearance of symptoms.<sup>4</sup>

The conclusion from these data is that the potential risk of peripheral neuropathy with statin therapy is very small, if it exists at all. Our neurology experts do not believe that such a relation exists and speculate that cases of peripheral neuropathy in patients taking statins are likely to be idiopathic in nature.<sup>9</sup> Given this background, it is reasonable to systematically evaluate patients who develop peripheral neuropathy symptoms while taking a statin. The first step would be to rule out secondary causes (ie, diabetes, renal insufficiency, alcohol abuse, vitamin B<sub>12</sub> deficiency, cancer, hypothyroidism, acquired immunodeficiency syndrome, Lyme disease, or heavy metal intoxication).<sup>2</sup> A second step would be to perform a neurologic physical examination and obtain diagnostic neurologic studies to quantify neurologic abnormalities.<sup>2</sup> If findings are supportive of peripheral neuropathy with no other identified cause, it would be appropriate to withdraw the statin (dechallenge), and if symptoms resolve, with the patient's permission, to restart therapy with another statin (rechallenge).<sup>4</sup> The goal would be to find a way to continue to provide the patient with the benefits of statin therapy, but without adverse consequences, if possible.

As for dementia and cognitive impairment, there is practically no evidence to support a link with statin therapy. In fact, statins may actually improve cognition.<sup>9</sup>

Table 5  
Recommendations for health professionals regarding neurologic disorders and statin therapy<sup>2,4,9</sup>

1. Routine neurologic monitoring of patients administering statin therapy for changes indicative of peripheral neuropathy or impaired cognition is not recommended.
2. Patients experiencing symptoms consistent with peripheral neuropathy while receiving a statin should be evaluated to rule out secondary causes (eg, diabetes mellitus, renal insufficiency, alcohol abuse, vitamin B<sub>12</sub> deficiency, cancer, hypothyroidism, acquired immunodeficiency syndrome, Lyme disease, or heavy metal intoxication).
3. If another etiology of the neurologic symptoms is not identified, it is appropriate to withdraw statin therapy for a period of 3–6 months to establish whether an apparent association with statin therapy exists.
4. If the patient's neurologic symptoms improve while off statin therapy, a presumptive diagnosis of statin-induced peripheral neuropathy might be made. However, because of the proven benefit of statin therapy, reinitiation of statin therapy should be considered with a different statin and dose.
5. If the patient's neurologic symptoms do not improve after statin therapy has been withdrawn for the specified period, statin therapy should be restarted based on a risk–benefit analysis.
6. If the patient experiences impaired cognition while receiving statin therapy it is appropriate to follow a similar course of evaluation as suggested above for peripheral neuropathy, ie, first rule out other etiologies, and if none are found, then withdraw the statin for 1–3 months. If improvement is not seen, statin therapy should be restarted based on a risk–benefit analysis.

The most noteworthy evidence addressing dementia is the large HPS, which studied 20,536 patients over a 5-year period and found no difference in the rate of cognitive impairment (based on a phone interview at the conclusion of the study) in patients receiving simvastatin versus placebo.<sup>4,9</sup> Similarly, the PROSPER study of patients aged 70–82 years reported no difference between placebo and pravastatin therapy.<sup>2,4,9</sup> One small proof-of-concept randomized, placebo-controlled clinical trial in patients with mild-to-moderate Alzheimer disease found that patients treated with atorvastatin actually showed improvement in state-of-the-art measures of cognition compared with those who were given placebo.<sup>2,9</sup> Additionally, several case-control and cohort studies suggest statin benefit in lowering the risk of Alzheimer disease and dementia.<sup>2</sup> Only a handful of case reports suggests worsening of cognition with statin therapy. While these might be idiosyncratic reactions, the existence of such reactions is not supported by any evidence from randomized clinical trials and cohort studies.

**Recommendations:** Table 5 shows our consensus recommendations to health professionals based on the evidence, interpretations, and assessments presented in this supplement regarding the neurologic system and statin safety.<sup>2,4,9</sup>

### Acknowledgments

The authors are grateful for the generous expert advice we received from Neil J. Stone, MD, Professor of Medicine, Northwestern University School of Medicine and Harold Bays, MD, President, Louisville Metabolic and Atherosclerosis Research Center.

1. Cohen DE, Anania FA, Chalasani N. An assessment of statin safety by hepatologists. *Am J Cardiol* 2006;97(suppl 8A):77C–81C.
2. Bays H. Statin safety: an overview and assessment of the data—2005. *Am J Cardiol* 2006;97(suppl 8A):6C–26C.
3. Jacobson TA. Statin safety: lessons from New Drug Applications for marketed statins. *Am J Cardiol* 2006;97(suppl 8A):44C–51C.
4. Law M, Rudnicka AR. Statin safety: evidence from the published literature. *Am J Cardiol* 2006;97(suppl 8A):52C–60C.
5. Cziraky MJ, Willey VJ, McKenney JM, Kamat SA, Fisher MD, Guyton JR, Jacobson TA, Davidson MH. Statin safety: An assessment using an administrative claims database. *Am J Cardiol* 2006;97(suppl 8A):61C–68C.
6. Thompson PD, Clarkson PM, Rosenson RS. An assessment of statin safety by muscle experts. *Am J Cardiol* 2006;97(suppl 8A):69C–76C.
7. Kasiske BL, Wanner C, O'Neill WC. An assessment of statin safety by nephrologists. *Am J Cardiol* 2006;97(suppl 8A):82C–85C.
8. Davidson MH, Clark JA, Glass LM, Kanumalla A. Statin safety: an appraisal from the Adverse Event Reporting System (AERS). *Am J Cardiol* 2006;97(suppl 8A):32C–43C.
9. Brass LM, Alberts MJ, Sparks L. An assessment of statin safety by neurologists. *Am J Cardiol* 2006;97(suppl 8A):86C–88C.