



Measure Title HEPATIC ENZYME MONITORING FOR STATIN USE: BEFORE INITIATING THERAPY

Disease State Hyperlipidemia Indicator Classification¹ Medication Monitoring

Strength of Recommendation² I

Physician Specialties Cardiovascular Disease, Family Practice, Gerontology, Internal Medicine

Clinical Rationale

Disease Burden

- In clinical trials and phase IV studies of Lovastatin, increases in aminotransferase enzyme (ALT) levels of greater than 3 times the upper limit of normal (ULN) were observed in 1 to 3% of patients.[1, 2]
• There are 232 reports of hepatitis associated with lovastatin, translating into a reporting rate of 9.7 cases/million patient-treatment years.[1]
• There are 22 reported cases of acute liver failure associated with lovastatin. This translates into a reporting rate of 1/1.14 million patient-treatment-years, approximately equal to the rate of idiopathic acute liver failure.[1]

Reason for Indicated Intervention or Treatment

- FDA recommendations indicate that liver function tests for statins should be performed for patients initiating statins and who take them regularly.[1]

Evidence supporting Intervention or Treatment

- In randomized controlled trials and comparative studies of statin therapy, elevated hepatic transaminases occurred in 0.5-2.0% of cases and are dose dependent.[3, 4]
• In a randomized controlled trial of lovastatin therapy, the 2 year incidence of serum transaminase elevation was 0.1 percent for 20 mg/day and 1.9 percent for 80 mg/day.[5]
• The American College of Cardiology considers the incidence of clinically important (>3 times upper limit of normal) transaminase elevations in the large statin trials to be the same for statin as for placebo. A recent meta-analysis of statin therapy supports this conclusion.[6, 7] Other trials also suggest that levels of transaminase may be similar between patients on statins and those not on statins,[8] while one review article goes as far as to say that this type of intervention is no longer appropriate due to the cost benefit ratio.[9]
• A retrospective review of statin therapy revealed that individuals with baseline elevations in LFTs on statin therapy were not at higher risk for statin-induced liver disease compared to individuals with baseline elevations in LFTs not on statin therapy.[10, 11]
• A large retrospective review of 385,000 HMO patients found that the majority of patients (65%) with alanine aminotransferase greater than 10 times the upper limit of normal experienced severe enzyme elevation within the first month after statin initiation, dose adjustment, and/ or additions of medications that might interact with statins. [12]

Clinical Recommendations

- The FDA recommends monitoring for potential hepatotoxicity before beginning statin treatment, 6 to 12 weeks following initiation of treatment, after a dosage change, and semiannually thereafter.[1]
- The American College of Cardiology/American Heart Association/National Heart Lung Blood Institute Clinical Advisory on the Use and Safety of Statin states: "Current labeling for all statins requires baseline measurements of liver function, including alanine transferase and aspartate transferase, although this is not agreed on by many liver experts and will likely undergo review in the future." [13] A 2004 update to these guidelines does not alter the recommendation.[14]

Source	Health Benchmarks, Inc.
Denominator	Continuously enrolled members who received at least a 1 prescription for statins during the measurement year.
Denominator Exclusion	Members with a prescription for a statin in the 1-365 days prior to the index date.
Numerator	Members who received at least one hepatic enzyme test in the 0-60 day period prior to the index prescription date (inclusive of the index date).
Interpretation of Score	High score implies better performance
Physician Attribution	Score all physicians (in the selected specialties) who saw the member 0- 60 days prior to the index date (inclusive of the index date).
External Files Required for Analysis	File name: <i>statin_den_medlist_2006.xls</i> Source: HBI Updated Annually
References	<ol style="list-style-type: none"> 1. Tolman, K.G., <i>The liver and lovastatin</i>. The American Journal of Cardiology, 2002. 89(12): p. 1374. 2. Maddrey, W.C., <i>Drug-induced hepatotoxicity 2005</i>. Journal Of Clinical Gastroenterology, 2005. 39(4): p. S83-S89. 3. Bradford, R.H., et al., <i>Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia</i>. Arch Intern Med, 1991. 151(1): p. 43-9. 4. Hsu, I., S.A. Spinler, and N.E. Johnson, <i>Comparative evaluation of the safety and efficacy of HMG-CoA reductase inhibitor monotherapy in the treatment of primary hypercholesterolemia</i>. Ann Pharmacother, 1995. 29(7-8): p. 743-59. 5. Bradford, R.H., et al., <i>Expanded Clinical Evaluation of Lovastatin (EXCEL) study results: two-year efficacy and safety follow-up</i>. Am J Cardiol, 1994. 74(7): p. 667-73. 6. de Denu, S., et al., <i>Statins and liver toxicity: A meta-analysis</i>. Pharmacotherapy, 2004. 24(5): p. 584-591. 7. <i>Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report</i>. Circulation, 2002. 106(25): p. 3143-421. 8. Smith, C.C., et al., <i>Screening for statin-related toxicity: the yield of transaminase and creatine kinase measurements in a primary care setting</i>. Arch Intern Med, 2003. 163(6): p. 688-92.

9. Sniderman, A.D., *Is there value in liver function test and creatine phosphokinase monitoring with statin use?* Am J Cardiol, 2004. **94**(9A): p. 30F-34F.
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11. Vuppalachchi, R., E. Teal, and N. Chalasani, *Patients with elevated baseline liver enzymes do not have higher frequency of hepatotoxicity from lovastatin than those with normal baseline liver enzymes.* Am J Med Sci, 2005. **329**(2): p. 62-5.
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13. Pasternak, R.C., et al., *ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins.* Stroke, 2002. **33**(9): p. 2337-41.
14. Grundy, S.M., et al., *Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines.* Circulation, 2004. **110**(2): p. 227-39.

CONFIDENTIAL

¹ **Indicator Classification** (Adapted from Health Plan Employer Data Information Set (HEDIS®) technical specifications)

Diagnosis	Measures applicable to patients receiving diagnostic workups for a symptom or condition that delineate appropriate laboratory or radiological testing to be performed (e.g. evaluation of thyroid nodule; pregnancy test in patients with vaginal bleeding or abdominal pain)
Effectiveness of Care	
Prevention	Measures applicable to asymptomatic individuals that are designed to prevent the onset of the targeted condition (e.g. immunizations).
Screening	Measures applicable to asymptomatic patients who have risk factors or pre-clinical disease, but in whom the condition has not become clinically apparent (e.g. pap smears; screening for elevated blood pressure).
Disease Management	Measures applicable to individuals diagnosed with a condition that are part of the treatment or management of the condition (e.g. cholesterol reduction in patients with diabetes; radiation therapy following breast conserving surgery; appropriate follow-up after acute event).
Medication Monitoring	Measures applicable to patients taking medications with narrow therapeutic windows and / or potential preventable significant side effects or adverse reactions (e.g. thyroid stimulating hormone (TSH) testing after levothyroxine dose change; hepatic enzyme monitoring for patients using antimycotic pharmacotherapy)
Medication Adherence	Measures applicable to patients taking medications for chronic conditions that are designed to assess patient adherence to medication (e.g. adherence to lipid lowering medication).
Utilization	Measures applicable to patients receiving treatment for a symptom or condition that advocate appropriate utilization of laboratory and pharmaceutical resources (e.g. conservative use of imaging for low back pain; inappropriate use of antibiotics for viral upper respiratory infection).

² Strength of Recommendation

Strength of Recommendation Based on a Body of Evidence

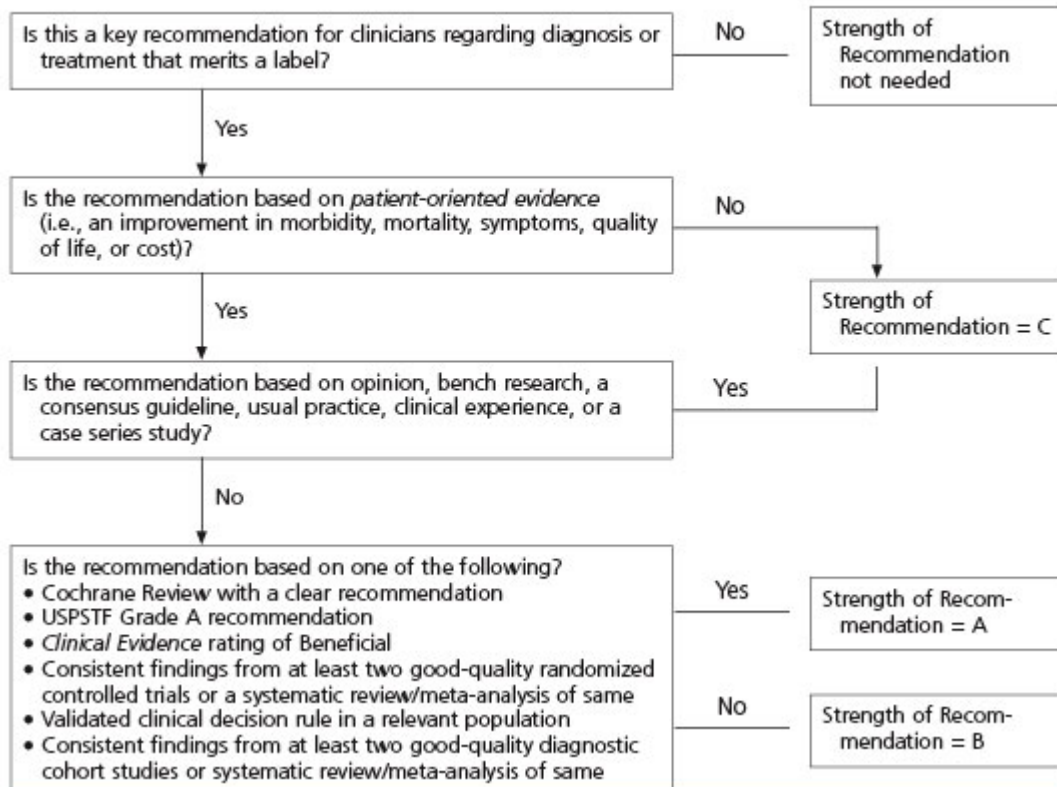


FIGURE 2. Algorithm for determining the strength of a recommendation based on a body of evidence (applies to clinical recommendations regarding diagnosis, treatment, prevention, or screening). While this algorithm provides a general guideline, authors and editors may adjust the strength of recommendation based on the benefits, harms, and costs of the intervention being recommended. (USPSTF = U.S. Preventive Services Task Force)