Is It Safe? Investigating the Use of Statins in Patients with Chronic Liver Disease

KIYA HARRISON, PHARM.D., BCPS
ASSISTANT PROFESSOR
UNIVERSITY OF OKLAHOMA COLLEGE OF PHARMACY
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Disclosures

• I have no relevant financial relationships or affiliations with commercial interests to disclose.
Objectives

At the completion of this activity, pharmacists will be able to:

1. Describe the controversy behind the use of statins in patients with chronic liver disease
2. Summarize the current literature addressing the safety and potential benefits of using statins in patients with chronic liver disease
3. Analyze statin therapy and appropriate monitoring parameters for patients with chronic liver disease, considering patient-specific factors

At the completion of this activity, technicians will be able to:

1. List adverse effects of statin medications

Overview

1. Patient case
2. Risk of cardiovascular disease in patients with chronic liver disease (CLD)
3. Safety of statins in the general population
4. Evidence for safety and potential benefits of statins in patients with CLD, with and without cirrhosis
5. Return to patient case
6. Clinical pearls
Terminology

• Chronic Liver Disease: broad term that encompasses anything that causes progressive damage/destruction to the liver (e.g. non-alcoholic fatty liver disease, hepatitis, alcoholic liver disease)

• Cirrhosis: irreversible scarring of the liver; an outcome of many forms of chronic liver disease

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Which of the following is true concerning the major controversy with statin use in chronic liver disease?

A. Fear of causing a secondary diabetes is a major concern with statin use in this population.

B. Patients with CLD do not produce enough cholesterol for statins to have any benefit.

C. Cardiovascular disease is rare in patients with CLD, so risks of statin therapy outweigh any potential benefits.

D. The concern for increased risk of hepatotoxicity in patients with CLD limits statin use in this population.

CLD = Chronic liver disease
Which of the following is true regarding the safety of statins in CLD?

A. Statins have been shown to increase the risk of mortality and decompensation in patients with CLD.
B. Statins have been proven to be safe to use in patients with CLD, with or without cirrhosis, at any Child-Pugh classification.
C. Total bilirubin may be a better biomarker for severe liver injury vs. aminotransferase elevations alone.
D. Atorvastatin has been proven to be the safest statin to use in patients with CLD.

CLD = Chronic liver disease

Patient Case

PATIENT RUSSELL VAY STANTIN
RS is a 63-year-old Caucasian male with a PMH of liver cirrhosis secondary to NASH, diabetes, HTN and HLD admitted for sepsis secondary to CAP. He was adequately fluid resuscitated and did not require pressors. He was initiated on CAP therapy with azithromycin and ceftriaxone and admitted to the general medicine floor.

**Home meds:** amlodipine 5 mg daily and glipizide 2.5 mg daily  
**Family history:** dad (died-MI at 65); mom (alive- DM)  
**SH:** Non-smoker, occasional alcohol  
**Physical exam:** General: A&O x 3; HEENT: EOMI, PERRLA; Pulmonary: tachypneic, decreased breath sounds; CV: RRR, no MRG; GI: soft, no ascites  
**Vitals:** BP 118/76, P 78, RR 27, T 38.2°C; Wt 94.2 kg, Ht 6’0”

### Labs:

<table>
<thead>
<tr>
<th>Na 134 mEq/L</th>
<th>Ca 9.8 mg/dL</th>
<th>Hgb 14.0 g/dL</th>
<th>Fasting lipid profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>K 4.4 mEq/L</td>
<td>Mg 2.0 mg/dL</td>
<td>Hct 44%</td>
<td>T. chol 159 mg/dL</td>
</tr>
<tr>
<td>Cl 102 mEq/L</td>
<td>AST 78 units/L</td>
<td>WBC 11.7 × 10³/mm³</td>
<td>Trig 92 mg/dL</td>
</tr>
<tr>
<td>CO₂ 23 mEq/L</td>
<td>ALT 95 units/L</td>
<td>Plt 91 × 10³/mm³</td>
<td>LDL 105 mg/dL</td>
</tr>
<tr>
<td>BUN 15 mg/dL</td>
<td>T. bili 1.8 mg/dL</td>
<td>PT 14.3 s</td>
<td>HDL 36 mg/dL</td>
</tr>
<tr>
<td>Scr 0.8 mg/dL</td>
<td>Albumin 3.0 g/dL</td>
<td>aPTT 47 s</td>
<td>A1C 7.3%</td>
</tr>
<tr>
<td>Glu 126 mg/dL</td>
<td>Troponin I 0.69 ng/mL</td>
<td>INR 1.4</td>
<td>NH₃ 56 mcg/dL</td>
</tr>
</tbody>
</table>

Cardiology is consulted due to concern for serially elevated troponins. The cardiologist assesses the elevations as possibly secondary to demand ischemia from respiratory distress due to CAP. However, NSTEMI cannot be ruled out considering the patient’s cardiovascular risk. He recommends to initiate aspirin and a statin in the setting of elevated troponins with plans to perform a left heart cath once the patient is stable.

The team questions this recommendation in light of the patient’s cirrhosis and asks for your opinion.

**Would you initiate a statin in this patient?**
Cardiovascular Disease (CVD) in Patients with CLD

Cardiovascular Disease

• About 785,000 Americans will experience a new coronary artery disease (CAD) event and approximately 470,000 will have a recurrent attack.

• Statins, HMG-CoA reductase inhibitors, are one of the cornerstones of treatment and are also used for primary or secondary prevention of atherosclerotic cardiovascular disease.

• Statins alter lipid metabolism to reduce risk of CAD and also exert pleiotropic effects (i.e. improving endothelial function, decreasing inflammation, stabilizing plaque).


https://medshadow.org/features/do‐statin‐drugs‐need‐a‐re‐think/
https://www.hopkinsmedicine.org/health/healthy_heart/stay_healthy/3-myths-about-cholesterol-lowering-statin-drugs
Chronic Liver Disease

- In 2013, chronic liver disease and cirrhosis was the 12th leading cause of death in the United States, accounting for >36,000 deaths.
- Most common causes: hepatitis C virus, alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD).
- Decompensated disease is associated with several complications.


Cardiovascular Risk in Patients with CLD

- Prevalence of CAD once considered to be low in liver disease.
- 2017 meta-analysis evaluating prevalence of CAD in liver disease.
  - Estimated a prevalence of 12.6%, similar to that of the general population.
- Now considered the leading cause of non-liver related mortality among patients with cirrhosis.

CVD Risk in Patients with Cirrhosis (Sorensen, et al)

- 10,154 patients with cirrhosis (predominantly alcoholic cirrhosis)
- 69% mortality within 12 years
- 51% cirrhosis-related
- 49% non-liver related causes
- 18% due to ischemic heart disease (leading cause)

Cardiovascular Disease Risk in Non-Alcoholic Fatty Liver Disease (NAFLD)

- Prevalence of cirrhosis secondary to NAFLD is increasing
- Headed toward becoming main underlying cause of liver transplantation
- Highest prevalence of NAFLD is among those with diabetes and obesity
  - Relationship with the metabolic syndrome

CVD = cardiovascular disease

Despite CVD risk, statins are under-prescribed in patients with CLD due to fear of hepatotoxicity

Survey of 937 providers from 138 academic centers

• 71% of providers were willing to prescribe statins to a 45-year-old woman with an LDL of 240 mg/dL
• Only 40% would prescribe a statin to a 55-year-old man with known CAD and LDL of 250 mg/dL and hepatitis C

Current manufacturer labeling: “Contraindicated in active liver disease or in patients with unexplained persistent elevations of serum transaminases.”

Safety of Statins in the General Population
Statin Hepatotoxicity Risk Factors and Biomarkers

• **Factors that may increase risk of statin hepatotoxicity or myopathy**
  - Using maximum doses
  - Drug-drug interactions mostly via P-glycoprotein, CYP 450 system, and OATPs (e.g. fibrates, azole antifungals, cyclosporine, lopinavir/ritonavir)
  - Elderly patients

• **Biomarkers of liver abnormalities**
  - ALT > 3 x ULN associated with moderate, temporary asymptomatic elevations
  - Occurs in up to 3% of patients on statins and usually not clinically significant
  - Increased bilirubin – superior marker of hepatotoxicity (rare, seen in < 1%)

• **Autoantibody-associated**
  - Markers: antinuclear antibody (ANA), anti-smooth muscle antibody (AMA), anti-mitochondrial antibody (AMiA)
Hy’s Law
• Hepatocellular injury that is severe enough to result in hyperbilirubinemia is indicative of a drug’s potential to cause serious liver injury
• Based on studies by Zimmerman et al.
  ◦ Found that drug-induced hepatocellular injury (elevated aminotransferases) PLUS jaundice had a poor prognosis
• Components of Hy’s law:
  ◦ **Hepatocellular injury**: AST/ALT > 3 x ULN
  ◦ **T. bilirubin elevations**: > 2 x ULN (without initial findings of obstruction)
  ◦ **No other causes** (e.g. other drugs, preexisting CLD)


Mechanism of Statin-Induced Liver Injury
• Not well understood
• Proposed mechanisms:
  ◦ Mitochondrial dysfunction
  ◦ Increase in mitochondrial superoxide (per in vitro studies)
  ◦ Mevalonic acid depletion during inhibition of cholesterol synthesis (animal studies)
  ◦ Apoptotic cell death
• Possible dose relationship
• Liver injury largely hepatocellular or cholestatic in nature or a mix

2012 FDA Labelling Updates for Statin Safety

“Labels have been revised to remove the need for routine periodic monitoring of liver enzymes in patients taking statins. The labels now recommend that liver enzyme tests should be performed before starting statin therapy and as clinically indicated thereafter. FDA has concluded that serious liver injury with statins is rare and unpredictable in individual patients, and that routine periodic monitoring of liver enzymes does not appear to be effective in detecting or preventing serious liver injury.”

https://www.fda.gov/drugs/drugsafety/ucm293101.htm#data
Drug-Induced Liver Injury Network Review of Statin Hepatotoxicity

- Patients enrolled if suspected liver injury due to any known drug, herbal, or supplement
- Excluded any other causes of liver injury (i.e. viral hepatitis, alcohol, pancreatitis, biliary, and metabolic liver disease)
- Patients followed for at least 6 months
- Roussel Uclaf Causality Assessment Method (RUCAM) score assigned to each case
- Results showed 1,188 patients between 2004-2012
  - Statins implicated in 61 cases (6%) but only 22 with > 50% likelihood per RUCAM (2%)
  - Statins were the only implicated drugs in 15 of the 22 cases
  - Mostly hepatocellular or cholestatic occurring between 34 days and 10 years
  - Autoimmune hepatitis also linked to cases

- Concluded that drug-induced liver injury from statins is rare


Summary of Statin Hepatotoxicity in General Population

- Several studies confirm that risk of liver injury from statins is rare and risk is greatly outweighed by the protective effect against thromboembolic stroke and coronary artery disease.
- Overall frequency of liver injury in general population estimated at 1.6 per 100,000 person-years of use
- National Lipid Association’s Statin Safety Task Force Liver Expert Panel stated that statin-associated elevations in aminotransferase levels are not indicative of liver damage or liver dysfunction

WHAT ABOUT PATIENTS WITH CHRONIC LIVER DISEASE??

# Safety of Statins in Patients with CLD (Without Cirrhosis)

## Safety of Pravastatin in CLD

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, randomized, placebo-controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Groups</strong></td>
<td>Pravastatin 80 mg vs. Placebo</td>
</tr>
<tr>
<td><strong>Inclusion Criteria</strong></td>
<td></td>
</tr>
</tbody>
</table>
  - > 18 y/o with chronic, well-compensated stable liver disease  
    - Chronic hepatitis C, NAFLD, or any other chronic liver disease  
    - LDL-C ≥ 100 mg/dL and triglycerides < 400 mg/dL  |
| **Exclusion Criteria** |  
  - ALT or AST > 5 x ULN, total bilirubin above normal, serum creatinine > 1.5 mg/dL, creatine kinase > 3 x ULN, albumin below normal, prothrombin time > 2 seconds, platelets below normal  
  - Ascites, jaundice or cirrhosis with a Child-Pugh score > 5  
  - Antiviral therapy for hepatitis B or C  
  - Prior lipid-lowering therapy ≥ 8 weeks  
  - Cardiovascular, cerebrovascular, renal or thyroid disease, or uncontrolled diabetes within 6 months  |
| **Endpoints**        |  
  - Primary efficacy: Percent change from baseline to week 12 in serum LDL-C  
  - Primary safety: Proportion with ≥ 1 ALT value ≥ 2 x ULN (for those with normal ALT at baseline) or doubling of baseline ALT for those with elevated ALT at baseline  |

ULN = upper limit of normal; NAFLD = non-alcoholic fatty liver disease
### Safety of Pravastatin in CLD: Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pravastatin (n=163)</th>
<th>Placebo (n=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years [mean (SD)]</td>
<td>49.8 (10.18)</td>
<td>49.9 (11.54)</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>77 (47.2%)</td>
<td>92 (56.4%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>140 (85.9%)</td>
<td>151 (92.6%)</td>
</tr>
<tr>
<td>African American</td>
<td>13 (8.0%)</td>
<td>3 (1.8%)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (3.1%)</td>
<td>4 (2.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (3.1%)</td>
<td>5 (3.1%)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>30.6 (6.05)</td>
<td>31.3 (6.30)</td>
</tr>
<tr>
<td>ALT (IU/L) [mean (SD)]</td>
<td>65.7 (44.77)</td>
<td>77.3 (49.01)</td>
</tr>
<tr>
<td>AST (IU/L) [mean (SD)]</td>
<td><strong>41.8 (24.73)</strong>*</td>
<td><strong>50.5 (31.51)</strong>*</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL) [mean (SD)]</td>
<td>0.61 (0.33)</td>
<td>0.63 (0.31)</td>
</tr>
<tr>
<td>Creatine kinase (IU/L) [mean (SD)]</td>
<td>157.9 (377.25)</td>
<td>122.5 (75.78)</td>
</tr>
</tbody>
</table>

*P < 0.0001

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### Safety of Pravastatin in CLD: Population, Cont.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pravastatin (n=163)</th>
<th>Placebo (n=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL) [mean (SD)]</td>
<td>138.8 (26.74)</td>
<td>140.5 (31.50)</td>
</tr>
<tr>
<td>HDL-C (mg/dL) [mean (SD)]</td>
<td>49.2 (13.71)</td>
<td>46.4 (10.39)</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL) [mean (SD)]</td>
<td>219 (33.4)</td>
<td>219.1 (37.66)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL) [mean (SD)]</td>
<td>161.2 (78.51)</td>
<td>166.2 (71.45)</td>
</tr>
<tr>
<td>Type of liver disease, n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAFLD</td>
<td><strong>105 (64.4%)</strong></td>
<td><strong>104 (63.8%)</strong></td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>38 (23.3%)</td>
<td>43 (26.4%)</td>
</tr>
<tr>
<td>Other*</td>
<td>20 (12.3%)</td>
<td>16 (9.8%)</td>
</tr>
</tbody>
</table>

*Hepatitis B (n=3), hemochromatosis (n=7), autoimmune hepatitis (n=5), past alcohol use (n=12), cirrhosis due to primary biliary cirrhosis or cryptogenic cirrhosis (n=9)

NAFLD = non-alcoholic fatty liver disease
Safety of Pravastatin in CLD: Efficacy Results

Primary Efficacy Endpoint: Percent Change from Baseline LDL-C (ITT Population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pravastatin*</th>
<th>Placebo*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL) [mean (SD)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>-32.57 (15.1)(^a)</td>
<td>0.82 (11.945)(^b)</td>
</tr>
<tr>
<td>Week 12</td>
<td>-30.61 (16.5)(^c)</td>
<td>2.70 (13.907)(^b)</td>
</tr>
<tr>
<td>Week 36</td>
<td>-25.85 (19.8)(^c)</td>
<td>-0.83 (19.994)(^b)</td>
</tr>
</tbody>
</table>

\(^a\)\(n = 153\); \(^b\)\(n = 154\); \(^c\)\(n = 155\)

Safety of Pravastatin in CLD: Safety Results

Primary Safety Endpoint: Proportion with > 1 ALT value > 2 x ULN

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pravastatin, ([n/N(%)])</th>
<th>Placebo, ([n/N(%)])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>2/160 (1.3%)</td>
<td>4/160 (2.5%)</td>
</tr>
<tr>
<td>Week 12</td>
<td>9/160 (5.6%)</td>
<td>11/160 (6.9%)</td>
</tr>
<tr>
<td>Week 36</td>
<td>12/160 (7.5%)</td>
<td>20/160 (12.5%)</td>
</tr>
</tbody>
</table>

\(P > 0.5\)

Primary Safety Endpoint: Doubling of ALT in those with Elevated ALT at Baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>Week</th>
<th>Pravastatin, ([n/N(%)])</th>
<th>Placebo, ([n/N(%)])</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD</td>
<td>12</td>
<td>3/58 (5.2%)</td>
<td>4/61 (6.6%)</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>4/58 (6.9%)</td>
<td>8/61 (13.1%)</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>12</td>
<td>0/21 (0%)</td>
<td>1/27 (3.7%)</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>2/21 (9.5%)</td>
<td>5/27 (18.5%)</td>
</tr>
</tbody>
</table>

\(P > 0.5\)

NAFLD = non-alcoholic fatty liver disease
Safety of Pravastatin in CLD: Conclusions

- High-dose pravastatin for hypercholesterolemia was efficacious and safe in those with chronic, well-compensated liver disease
- ALT elevations that doubled from baseline were not statistically different between the groups


Safety of Pravastatin in CLD: Limitations

- Included only Child-Pugh Class A patients (exclusion criteria limits generalizability)
- Only moderate intensity statin assessed (and only 1 statin used)
- Lacking adequate representation of the various types of chronic liver disease
- Underpowered to detect differences in ALT elevations
### Safety of Statins in Hepatitis C Patients

**Khorashadi S, et al, 2006 (n= 830)**

<table>
<thead>
<tr>
<th>Design</th>
<th>Retrospective study using data from Veterans Affairs Health Care System (12 month study)</th>
</tr>
</thead>
</table>
| **Treatment Groups** | Cohort 1: HCV positive patients + statin  
Cohort 2: HCV positive patients + no statin  
Cohort 3: HCV negative patients + statin |
| **Population** | Median age 54, 98% male  
Simvastatin and lovastatin most common |
| **Endpoints** | Risk for developing hepatotoxicity (Mild-moderate= AST/ALT up to 10 x ULN; Severe= T. bili > 3 mg/dL or AST/ALT > 10 x ULN) |
| **Results** | ↑ mild-mod. AT increases in HCV + statin vs. HCV + no statin*  
↓ severe AT increases in HCV + statin vs. HCV + no statin*  
Overall incidence similar between groups |
| **Limitations** | All male patients  
No breakdown of results based on statin type |

*P < 0.05

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### Additional Evidence For Safe Use of Statins in CLD

**GREACE trial, 2010 (n=437)**

<table>
<thead>
<tr>
<th>Design</th>
<th>Post-hoc analysis of a prospective survival study in patients with CAD</th>
</tr>
</thead>
</table>
| **Treatment Groups** | Statin vs. no statin  
Compared in patients w/ and w/o abnormal ATs (AST/ALT up to 3 x ULN) |
| **Population** | Mean age 60, LDL > 100 mg/dL  
Mostly atorvastatin (moderate)  
Majority considered to have NAFLD |
| **Endpoints** | 1. First recurrent CV event  
2. Effects of statins on ATs and eGFR |
| **Results** | Greater ↓ in ATs in statin group for patients with moderately abnormal ATs*  
CV events occurred in 10% of statin group vs. 30% of non-statin group* |
| **Limitations** | CLD not diagnosed but presumed to be NAFLD  
Excluded hepatitis B/C, alcoholic liver disease |

*P < 0.0001
Retrospective Study of Risk of Statin Hepatotoxicity in Patients with Elevated Baseline Liver Enzymes

**Treatment groups**
- Cohort 1: elevated baseline enzymes (AST > 40 IU/L or ALT > 35 IU/L) who received statin
- Cohort 2: without elevated liver enzymes who received statin
- Cohort 3: with elevated liver enzymes who did not receive statin

**Endpoints**
- Mild to moderate elevations:
  - AST/ALT up to 10 x ULN in patients with normal baseline enzyme levels
  - Up to 10-fold increase from baseline AST/ALT in patients with elevated liver enzyme levels at baseline
- Severe elevations:
  - T. bilirubin > 3 mg/dL (regardless of baseline transaminase level)
  - Increased AST/ALT > 10 x ULN in patients with normal baseline enzymes or > 10-fold elevations from baseline in patients with elevated liver enzyme levels at baseline


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Table 2. Frequency of Varying Degrees of Elevations in Liver Biochemistries Over a 6-Month Period in 3 Study Cohorts

<table>
<thead>
<tr>
<th></th>
<th>Cohort 2 (n = 1437)</th>
<th>Cohort 1 (n = 342)</th>
<th>Cohort 3 (n = 2245)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-moderate elevations in liver biochemistries</td>
<td>1.9%</td>
<td>4.7%</td>
<td>6.4%</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = 0.002</td>
<td><em>P</em> = 0.2</td>
<td></td>
</tr>
<tr>
<td>Severe elevations in liver biochemistries</td>
<td>0.2%</td>
<td>0.6%</td>
<td>0.4%</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = 0.2</td>
<td><em>P</em> = 0.6</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Cohort 1: individuals with elevated baseline liver enzymes who were placed on a statin. Cohort 2: Individuals with normal baseline liver enzymes who were placed on a statin. Cohort 3: Individuals with elevated liver enzymes but not placed on a statin.

Retrospective Study of Risk of Statin Hepatotoxicity in Patients with Elevated Baseline Liver Enzymes

Table 4. Change in Transaminases Within 6 Months After Starting a Statin Stratified by Type of Statin Prescribed

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin (n = 819)</th>
<th>Simvastatin (n = 904)</th>
<th>Other statins* (n = 56)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median dose per day</td>
<td>10 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td></td>
</tr>
<tr>
<td>Mean dose per day</td>
<td>14 ± 22</td>
<td>17 ± 41</td>
<td>23 ± 9</td>
<td></td>
</tr>
<tr>
<td>Baseline AST (IU/L)</td>
<td>28 ± 21</td>
<td>29 ± 23</td>
<td>24 ± 8</td>
<td>0.3</td>
</tr>
<tr>
<td>Baseline ALT (IU/L)</td>
<td>26 ± 18</td>
<td>25 ± 17</td>
<td>32 ± 28</td>
<td>0.2</td>
</tr>
<tr>
<td>Proportion with elevated AST and/or ALT at baseline</td>
<td>18%</td>
<td>21%</td>
<td>13%</td>
<td>0.2</td>
</tr>
<tr>
<td>Incidence of liver biochemistries elevations*</td>
<td>2%</td>
<td>3.1%</td>
<td>4.3%</td>
<td>0.4</td>
</tr>
<tr>
<td>Change in AST (IU/L)</td>
<td>8 ± 80</td>
<td>34 ± 628</td>
<td>19 ± 88</td>
<td>0.3</td>
</tr>
<tr>
<td>Change in ALT (IU/L)</td>
<td>22 ± 98</td>
<td>42 ± 329</td>
<td>26 ± 80</td>
<td>0.4</td>
</tr>
<tr>
<td>Proportion that discontinued statin during follow-up (%)</td>
<td>10%</td>
<td>11.5%</td>
<td>8.5%</td>
<td>0.5</td>
</tr>
</tbody>
</table>

NOTE. Table represents cohorts 1 and 2 combined.
*Other statins include fluvastatin in 49 patients and pravastatin in 7 patients.
*This represents the combination of mild-moderate and severe elevations in liver biochemistries.


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Retrospective Study of Risk of Hepatotoxicity from Lovastatin in Patients with Elevated Baseline Liver Enzymes

Table 2. The Frequency of Varying Degrees of Elevations in Liver Biochemistries during the Follow-Up in Three Study Cohorts*

<table>
<thead>
<tr>
<th></th>
<th>Cohort 2 (n = 620)</th>
<th>Cohort 1 (n = 135)</th>
<th>Cohort 3 (n = 2644)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-moderate elevations in liver biochemistries*</td>
<td>3.0%</td>
<td>6.6%</td>
<td>11%</td>
</tr>
<tr>
<td>Severe elevations in liver biochemistries*</td>
<td>0.3%</td>
<td>0%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Hy's rule*</td>
<td>0%</td>
<td>0%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Hy's Rule: AST/ALT level > 3 x ULN and T. bili > 2 x ULN


T. bili = total bilirubin; ULN = upper limit of normal
Summary of Statin Safety in CLD

**Positive Outcomes**

• Statin therapy decreases LDL with mild-moderate increases in ATs
• Statin therapy does not seem to significantly increase risk of severe hepatotoxicity
• Potential decrease in risk of CV events (could be secondary to NASH/NAFLD patients included in studies)

**Data Limitations**

• Largely limited to Child-Pugh Class A, those with mild-moderate AT elevations at baseline
• Concern for prescribing biases in retrospective studies
• Unclear if statin choice and dose makes a difference in outcomes

AT = aminotransferases; CLD = chronic liver disease; NASH: non-alcoholic steatohepatitis
CV = cardiovascular; NAFLD = non-alcoholic fatty liver disease

Safety of Statins in Patients with Cirrhosis
### Statin Use in Patients with Cirrhosis

<table>
<thead>
<tr>
<th>Design</th>
<th>Retrospective cohort study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Groups</strong></td>
<td><strong>• Patients taking statins for ≥ 3 months</strong>&lt;br&gt;<strong>• Patients not taking statins (1:2 matching with treatment group by age, gender, and Child-Pugh)</strong></td>
</tr>
<tr>
<td><strong>Inclusion Criteria</strong></td>
<td><strong>• ≥ 18 y/o with biopsy-proven cirrhosis</strong></td>
</tr>
<tr>
<td><strong>Exclusion Criteria</strong></td>
<td><strong>• Not meeting inclusion criteria</strong>&lt;br&gt;<strong>• Lack of statin use for 3 months</strong></td>
</tr>
<tr>
<td><strong>Endpoints</strong></td>
<td><strong>• Primary: All-cause mortality</strong>&lt;br&gt;<strong>• Secondary: Decompensation in baseline-compensated patients</strong>&lt;br&gt;<strong>• Defined as ascites, jaundice/bilirubin &gt; 2.5 mg/dL, and/or hepatic encephalopathy</strong></td>
</tr>
</tbody>
</table>


### Statin Use in Patients with Cirrhosis: Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statin users (n=81)</th>
<th>Controls (n=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>44 (54.32)</td>
<td>88 (54.32)</td>
</tr>
<tr>
<td>Age, mean years (SD)</td>
<td>59.79 (10.91)</td>
<td>59.64 (10.60)</td>
</tr>
<tr>
<td>Type of liver disease, n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NASH*</td>
<td>35 (43.21)</td>
<td>41 (25.31)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>18 (22.22)</td>
<td>55 (33.95)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>18 (22.22)</td>
<td>39 (24.07)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>2 (2.47)</td>
<td>10 (6.17)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>3 (3.70)</td>
<td>6 (3.70)</td>
</tr>
<tr>
<td>Cardiac cirrhosis</td>
<td>4 (4.94)</td>
<td>6 (3.70)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (9.88)</td>
<td>16 (9.88)</td>
</tr>
<tr>
<td>Child-Pugh mean score (SD)</td>
<td>6.14 (1.35)</td>
<td>6.26 (1.38)</td>
</tr>
<tr>
<td>Class A, n(%)</td>
<td>57 (70.37)</td>
<td>114 (70.37)</td>
</tr>
<tr>
<td>Class B or C, n(%)</td>
<td>24 (29.63)</td>
<td>48 (29.63)</td>
</tr>
</tbody>
</table>

*P < 0.0001

Statin Use in Patients with Cirrhosis: Population, Cont.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statin users (n=81)</th>
<th>Controls (n=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular carcinoma, n (%)</td>
<td>9 (11.11)</td>
<td>20 (12.34)</td>
</tr>
<tr>
<td>MELD, mean (SD)</td>
<td>10.96 (4.02)</td>
<td>11.68 (4.61)</td>
</tr>
<tr>
<td>Albumin, mean (SD)</td>
<td>3.49 (0.77)</td>
<td>3.41 (0.67)</td>
</tr>
<tr>
<td>Presence of varices, n(%)</td>
<td>19 (36.54)</td>
<td>27 (35.06)</td>
</tr>
<tr>
<td>CAD, n(%)*</td>
<td>35 (43.21)</td>
<td>20 (12.35)</td>
</tr>
<tr>
<td>Diabetes, n(%)*</td>
<td>45 (55.56)</td>
<td>50 (30.86)</td>
</tr>
<tr>
<td>LDL, mean (SD)</td>
<td>91.69 (38.79)</td>
<td>84.20 (37.41)</td>
</tr>
</tbody>
</table>

*P < 0.0001


MELD = model for end-stage liver disease
CAD = coronary artery disease

Statin Use in Patients with Cirrhosis: Primary Endpoint

![Kaplan Meier Curve for Mortality](image)

Median Time to Death, years

- Statin: 10.8
- Control: 6.3

P = 0.06

Statin Use in Patients with Cirrhosis: Primary Endpoint (Child-Pugh A)

Median Time to Death, years

<table>
<thead>
<tr>
<th></th>
<th>Statin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14.4</td>
<td>7</td>
</tr>
</tbody>
</table>

P = 0.01


Statin Use in Patients with Cirrhosis: Additional Results

• Most common statins used: simvastatin (49.4%) and atorvastatin (29.6%)

• Overall, 37% of statin group died and 2.5% underwent liver transplantation vs. 50.6% and 17.9% of the control group

• Univariate analysis
  ◦ Showed trend toward lower mortality in patients on statins (HR 0.66, P = 0.05)
  ◦ Coronary artery disease, HCC and MELD score were significantly associated with higher mortality

• Multivariate analysis with a Cox proportional hazards model, controlling for MELD score, coronary artery disease, diabetes, NASH and HCC
  ◦ Statin use became significantly associated with lower mortality (HR 0.53, P = 0.01)
  ◦ Coronary artery disease, higher MELD, HCC and NASH were associated with higher mortality


MELD = model for end-stage liver disease; HR = hazard ratio
NASH = non-alcoholic steatohepatitis; HCC = hepatocellular carcinoma
Statin Use in Patients with Cirrhosis: Occurrence of Decompensation

- Of patients compensated at baseline, occurrence of decompensation was **30.0 % of patients in the statin users compared to 40.5% in the control group, P = 0.04**
- Univariate analysis: statin use not significantly associated with hepatic decompensation (HR 0.63, P = 0.07)
- Multivariate analysis: statin use **associated with lower risk of decompensation** (HR 0.58, P = 0.04)
- Statin group had a statistically significantly lower occurrence of ascites vs. no statin (16% vs. 31%, P = 0.017)
- Variceal hemorrhage was significantly less likely to occur in patients not on statins (statin 11% vs. no statin 2%, P = 0.02)
- No statistically significant difference in the development of jaundice or hepatic encephalopathy


Statin Use in Patients with Cirrhosis: Study Conclusions

- Decreased mortality with statin therapy when controlling for potential confounders (i.e. CAD, diabetes, HCC, NASH, and MELD score)
- CAD, HCC and NASH associated with increased mortality
- Statin use associated with lower risk of decompensation per multivariate analysis
- Possible that the lower mortality rate is associated with reduced rate of clinical decompensation (driven by lower occurrence of ascites?)
- Overall, the use of statins in **compensated cirrhosis** does not increase mortality risk and may potentially be beneficial

Kumar S, et al. Dig Dis Sci 2014;59:1958-65. MELD = model for end-stage liver disease; CAD = coronary artery disease; NASH = non-alcoholic steatohepatitis; HCC = hepatocellular carcinoma
Statin Use in Patients with Cirrhosis: Study Limitations

- Retrospective study – bias in prescribing patterns
- No evaluation of whether type or intensity of statin impacted results
- Decrease in decompensation potentially due to fact that majority of patients had NASH
- Majority Child-Pugh Class A

Addition of Simvastatin for Prevention of Variceal Re-bleeding

**Abraldes, et al, 2016 (n= 147)**

<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th>Multicenter, randomized controlled trial</th>
</tr>
</thead>
</table>
| **Treatment Groups** | • Simvastatin (target dose 40 mg/day)  
• Placebo |
| **Inclusion Criteria** | • 18-80 y/o; liver cirrhosis; variceal bleed within 5-10 days with plan to start standard treatment for prevention of re-bleeding |
| **Exclusion Criteria** | • Multifocal HCC; Scr > 2 mg/dL; Child-Pugh > 13; HIV on protease inhibitors; bleed due to gastric varices; complete portal vein thrombosis; portosystemic shunt |
| **Endpoints** | • Primary: composite of all-cause re-bleeding or all-cause death  
• Secondary: all-cause death; all-cause re-bleeding |
### Addition of Simvastatin for Prevention of Variceal Re-bleeding: Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Simvastatin (n= 69)</th>
<th>Placebo (n= 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>45 (65.2)</td>
<td>53 (67.9)</td>
</tr>
<tr>
<td>Age, mean years (SD)</td>
<td>57.42 (11.31)</td>
<td>57.6 (10.59)</td>
</tr>
<tr>
<td>Etiology of Cirrhosis, n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>49 (71)</td>
<td>55 (71.4)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>19 (27.5)</td>
<td>17 (22.1)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1 (1.4)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Primary Biliary Cirrhosis</td>
<td>3 (4.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NASH</td>
<td>1 (1.4)</td>
<td>4 (5.2)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (7.2)</td>
<td>7 (9.1)</td>
</tr>
<tr>
<td>Liver Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child-Pugh mean score (SD)</td>
<td>7.93 (1.64)</td>
<td>7.68 (1.78)</td>
</tr>
<tr>
<td>Class A/B/C, (%)</td>
<td>15/68/17</td>
<td>24/62/14</td>
</tr>
<tr>
<td>MELD Score, mean (SD)</td>
<td>10.15 (4.40)</td>
<td>10.03 (5.32)</td>
</tr>
</tbody>
</table>

**Addition of Simvastatin for Prevention of Variceal Re-bleeding: Population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Simvastatin (n= 69)</th>
<th>Placebo (n= 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis Complications, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascites</td>
<td>26 (37.7)</td>
<td>22 (28.2)</td>
</tr>
<tr>
<td>Refractory ascites</td>
<td>6 (8.7)</td>
<td>4 (5.1)</td>
</tr>
<tr>
<td>Edema</td>
<td>11 (15.9)</td>
<td>20 (25.6)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>2 (2.9)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>3 (4.3)</td>
<td>5 (6.4)</td>
</tr>
<tr>
<td>Lab Data, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>2.34 (2.58)</td>
<td>2.20 (2.60)</td>
</tr>
<tr>
<td>AST</td>
<td>78.18 (87.83)</td>
<td>67.39 (50.99)</td>
</tr>
<tr>
<td>ALT</td>
<td>48.77 (47.38)</td>
<td>41.39 (33.09)</td>
</tr>
<tr>
<td>LDL, median</td>
<td>69</td>
<td>79</td>
</tr>
</tbody>
</table>

Addition of Simvastatin for Prevention of Variceal Re-bleeding: Primary Outcome

Addition of Simvastatin for Prevention of Variceal Re-bleeding: Secondary Outcome
Addition of Simvastatin for Prevention of Variceal Re-bleeding: Safety

• One patient was withdrawn from the study due to > 3-fold increase in liver transaminases
• Two patients experienced rhabdomyolysis
  ◦ Both in the simvastatin group
  ◦ Occurred at days 15 and 85 after initiation of statin
  ◦ Peak creatine kinase levels of 7823 and 3500 IU/L
  ◦ Both recovered after discontinuing the statin
• Both patients had deteriorated liver function at baseline: T. bili > 5 mg/dL


Effects of Hypercholesterolemia and Statin Exposure on Survival in Cirrhosis

• Retrospective cohort study of VA patients with newly diagnosed cirrhosis
  ◦ > 70% Child-Pugh A and median MELD score of 9
• Compared patients with prior statin exposure to statin-naïve patients
• Found that statins were associated with an 8-8.7% annual reduction in mortality
  ◦ Appeared to primarily be due to reduction in hepatic events except for NAFLD/NASH where reduction in both hepatic events and major adverse cardiovascular events (MACE) was seen
  ◦ In statin-naive patients, every 10 mg/dL increase in baseline total cholesterol was associated with a 3.6% reduction in mortality
    ◦ Serum cholesterol are markers of hepatic synthetic function
• Effects seen in Child-Pugh A/B patients, not in Child-Pugh C

Kaplan DE, et al. Gastroenterology 2019. https://doi.org/10.1053/j.gastro.2019.01.026 MELD = model for end-stage liver disease NASH: non-alcoholic steatohepatitis; NAFLD = non-alcoholic fatty liver disease
Summary of Statin Safety in Patients with Cirrhosis

• Statins seem to be relatively safe and effective in patients with cirrhosis and may even have benefits (decreased mortality and decompensation)

• These effects seem to be limited to Child-Pugh Class A/B patients with compensated cirrhosis and those with low MELD scores

• Concern for increased harm in those with severe hepatic dysfunction (elevated total bilirubin)

Benefits of Statins in CLD
Potential Benefits of Statin Use in CLD

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal hypertension</td>
<td>Decrease oxidative stress and inflammation at the vessel wall, antithrombotic properties, and improve endothelial function (increase nitric oxide production)</td>
</tr>
</tbody>
</table>
| Hepatocellular carcinoma         | • In vitro animal studies: anti-proliferative, pro-apoptotic, anti-angiogenic, immunomodulatory, and anti-infective properties that prevent cancer growth  
• 2013 meta-analysis showed 41% overall reduction in risk of HCC |
| Hepatitis B/C                    | • Hepatitis C – associated with reduced risk of fibrosis progression, cirrhosis, decompensation, and HCC  
• Hepatitis B – associated with decreased cirrhosis and decompensation |
| Sepsis                           | • May increase ability of phagocytes to create extracellular traps  
• Retrospective study showed decrease in rate of infection (peritonitis/SBP and pneumonia) or death |
| Non-alcoholic fatty liver disease | Associated with less steatosis and decrease in fibrosis |

HCC = hepatocellular carcinoma

Proposed Mechanisms for Statin Benefit in CLD

Statins in pre-clinical research

- Statins
- KLF-2 system
- Rho-A/Ras pathway
- HSC
  - Suppress paracrine activation
  - ↓ collagen production
  - ↓ proliferation activity and turnover myofibroblast
- Endothelial cell
  - ↑ eNOS, NO production, thrombomodulin, CNP
  - ↓ response to ET-1
  - ↓ hepatic vascular resistance
- Hepatocyte
  - ↓ inflammatory markers and inflammation in histology
  - ↓ NASH-induced PPAR-γ depletion

Systematic Review and Meta-Analysis of Statin Benefits in CLD

Risk of Cirrhosis or Fibrosis Progression
- Non-significant 58% lower risk ($I^2=99\%)$
- Overall confidence in estimate was very low

Risk of Decompensation
- 46% lower risk, especially if compensated at baseline ($I^2=0\%)$
- Overall confidence in estimate was moderate

Risk of Mortality
- 39% lower risk ($I^2=77\%)$
- Overall confidence in estimate was moderate

Portal Hypertension
- 27% lower risk of rebleeding or failure to improve portal hypertension ($I^2=0\%)$
- Overall confidence in estimate was moderate


Return to Patient Case
PATIENT RUSSELL VAY STANTIN
RS is a 63-year-old Caucasian male with a PMH of liver cirrhosis secondary to NASH, diabetes, HTN and HLD admitted for sepsis secondary to CAP. He was adequately fluid resuscitated and did not require pressors. He was initiated on CAP therapy with azithromycin and ceftriaxone and admitted to the general medicine floor.

**Home meds:** amlodipine 5 mg daily and glipizide 2.5 mg daily  
**Family history:** dad (died-MI at 65); mom (alive-DM)  
**SH:** Non-smoker, occasional alcohol  
**Physical exam:** General: A&O x 3; HEENT: EOMI, PERRLA; Pulmonary: tachypneic, decreased breath sounds; CV: RRR, no MRG; Gl: soft, no ascites  
**Vitals:** BP 118/76, P 78, RR 27, T 38.2°C; Wt 94.2 kg, Ht 6'0"  
**Labs:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Fasting lipid profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>134 mEq/L</td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>4.4 mEq/L</td>
<td></td>
</tr>
<tr>
<td>Ca</td>
<td>9.8 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Mg</td>
<td>2.0 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Hgb</td>
<td>14.0 g/dL</td>
<td></td>
</tr>
<tr>
<td>Hct</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>78 units/L</td>
<td>Trig 92 mg/dL</td>
</tr>
<tr>
<td>ALT</td>
<td>95 units/L</td>
<td>LDL 105 mg/dL</td>
</tr>
<tr>
<td>WBC</td>
<td>11.7 x 10^3/mm³</td>
<td></td>
</tr>
<tr>
<td>Plt</td>
<td>91 x 10^3/mm³</td>
<td></td>
</tr>
<tr>
<td>CO₂</td>
<td>23 mEq/L</td>
<td></td>
</tr>
<tr>
<td>T. chol</td>
<td>159 mg/dL</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>92 mg/dL</td>
<td></td>
</tr>
<tr>
<td>T. bili</td>
<td>1.8 mg/dL</td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>14.3 s</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>36 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.0 g/dL</td>
<td></td>
</tr>
<tr>
<td>aPTT</td>
<td>47 s</td>
<td></td>
</tr>
<tr>
<td>A1C</td>
<td>7.3%</td>
<td></td>
</tr>
<tr>
<td>Glu</td>
<td>126 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Troponin I</td>
<td>0.69 ng/mL</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>NH₃</td>
<td>56 mcg/dL</td>
<td></td>
</tr>
</tbody>
</table>

Cardiology is consulted due to concern for serially elevated troponins. The cardiologist assesses the elevations as possibly secondary to demand ischemia from respiratory distress due to CAP. However, NSTEMI cannot be ruled out considering the patient’s cardiovascular risk. He recommends to initiate aspirin and a statin in the setting of elevated troponins with plans to perform a left heart cath once the patient is stable.

The team questions this recommendation in light of the patient’s cirrhosis and asks for your opinion.

**Would you initiate a statin in this patient?**
Assessment of Patient RS

- Child-Pugh score of 6 places RS in category A
- MELD score of 15 represents a 6% risk of mortality in 3 months
- BMI is 28.1
- ASCVD score = 20.9% placing patient in the high risk category
- Family history of death due to MI
- Total bilirubin < 2 mg/dL
- Age slightly higher than those included in statin safety studies
- Could potentially benefit from decrease in risk of mortality and decompensation of cirrhosis
- Etiology of NASH may further increase likelihood of mortality benefit due to decrease in major adverse cardiovascular events

Plan for Patient RS

- Would agree to initiate a statin in this patient.
- Can select a moderate intensity statin (e.g. atorvastatin 20 mg)
- Close follow-up monitoring of aminotransferases and total bilirubin
- Also monitor for drug interactions and any symptoms of myopathy
Which of the following is true concerning the major controversy with statin use in chronic liver disease?

A. Fear of causing a secondary diabetes is a major concern with statin use in this population.
B. Patients with CLD do not produce enough cholesterol for statins to have any benefit.
C. Cardiovascular disease is rare in patients with CLD, so risks of statin therapy outweigh any potential benefits.
D. Concern for increased risk of hepatotoxicity in patients with CLD limits statin use in this population.

CLD = Chronic liver disease

Which of the following is true regarding the safety of statins in CLD?

A. Statins have been shown to increase the risk of mortality and decompensation in patients with CLD.
B. Statins have been proven to be safe to use in patients with CLD, with or without cirrhosis, at any Child-Pugh classification.
C. Total bilirubin may be a better biomarker for severe liver injury vs. aminotransferase elevations alone.
D. Atorvastatin has been proven to be the safest statin to use in patients with CLD.

CLD = Chronic liver disease
Clinical Pearls

• Consider using a statin when indicated in patients with CLD or compensated cirrhosis
  ◦ Safest use may be in patients with Child-Pugh Class A disease
• Type and dose of statin not well defined
  ◦ Most studies used moderate intensity
• Avoid in decompensated cirrhosis, especially if baseline total bilirubin > 2 (some experts recommend cutoff of > 3)
• Screen for and avoid drug-drug interactions that may increase serum statin concentration
• May avoid in elderly patients > 75, since most of these studies did not include this age group
• Monitor aminotransferases and total bilirubin more frequently and for signs/symptoms of adverse effects (e.g. myopathy)

Future Outlook

• Need more prospective studies to explore safety in Child-Pugh classes B/C and higher MELD scores
• Also need more studies to confirm association between statins and CLD benefits
• Comparisons between statins and dosing strategies
Is it Safe? The Use of Statins in Patients with Chronic Liver Disease

KIYA HARRISON, PHARM.D., BCPS
ASSISTANT PROFESSOR
UNIVERSITY OF OKLAHOMA COLLEGE OF PHARMACY
2019 OSHP ANNUAL SPRING MEETING