EFFECT OF STATINS, EZETIMIBE AND OTHER LIPID LOWERING DRUGS IN LIVER DISEASES

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LIPID LOWERING DRUGS

- HMG CoA reductase (hydroxymethylglutaryl CoA reductase) inhibitors (Statins)
- Fibric acid derivatives
- Bile acid sequestrants
- Cholesterol absorption inhibitors
- Nicotinic acid

differ with respect to mechanism of action and to the degree and type of lipid lowering
## Average effects of different classes of lipid lowering drugs on serum lipids

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Serum LDL cholesterol</th>
<th>Serum HDL cholesterol</th>
<th>Serum triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile acid sequestrants</td>
<td>↓ 15 to 30 percent</td>
<td>0 to slight increase</td>
<td>No change*</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>↓ 10 to 25 percent</td>
<td>↑ 15 to 35 percent</td>
<td>↓ 25 to 30 percent</td>
</tr>
<tr>
<td>HMG CoA reductase inhibitors</td>
<td>↓ 20 to 60 percent</td>
<td>↑ 5 to 10 percent</td>
<td>↓ 10 to 33 percent</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>↓ 10 to 15 percent</td>
<td>↑ 15 to 25 percent</td>
<td>↓ 35 to 50 percent</td>
</tr>
<tr>
<td>Fenofibrate (micronized form)</td>
<td>↓ 6 to 20 percent</td>
<td>↑ 18 to 33 percent</td>
<td>↓ 41 to 53 percent</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitors</td>
<td>↓ 17 percent</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Neomycin</td>
<td>↓ 20 to 25 percent</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Omega 3 fatty acids•</td>
<td>↑ 4 to 49 percent</td>
<td>↑ 5 to 9 percent</td>
<td>↓ 23 to 45 percent</td>
</tr>
</tbody>
</table>
Cholesterol-lowering drugs and liver: the dilemma

MAY CAUSE LIVER DAMAGE

USED WITH LIVER DAMAGE

Ferri et al, EJCI 2008
Cholesterol-lowering drugs used in different conditions

- Hypertransaminasemia
- NAFLD
- Chronic non-viral hepatitis
- Viral hepatitis
- Cholestatic liver diseases
- ALD
- Liver transplant
- Gallstone disease
Statins

**Simvastatin**

Chemical Formula: $\text{C}_{25}\text{H}_{38}\text{O}_5$

Molecular Weight: 418.6

Elemental Analysis: C, 71.74; H, 9.15; O, 19.11

**Lovastatin**

Chemical Formula: $\text{C}_{27}\text{H}_{36}\text{O}_5$

Molecular Weight: 404.5

Elemental Analysis: C, 71.26; H, 8.97; O, 19.77

**Pravastatin**

Chemical Formula: $\text{C}_{23}\text{H}_{31}\text{O}_6$

Molecular Weight: 406.5

Elemental Analysis: C, 67.90; H, 8.47; O, 23.61

**Atorvastatin**

Chemical Formula: $\text{C}_{24}\text{H}_{25}\text{FNNaO}_4$

Molecular Weight: 433.4

Elemental Analysis: C, 66.50; H, 5.81; F, 4.38; N, 3.23; Na, 5.30; O, 14.76

**Fluvastatin**

Chemical Formula: $\text{C}_{22}\text{H}_{24}\text{FNNaO}_4$

Molecular Weight: 433.4

Elemental Analysis: C, 66.50; H, 5.81; F, 4.38; N, 3.23; Na, 5.30; O, 14.76

**Rosuvastatin**

Chemical Formula: $\text{C}_{24}\text{H}_{24}\text{FNaO}_5$

Molecular Weight: 486.2

Elemental Analysis: C, 24.87; H, 5.86; F, 3.28; N, 8.73; O, 19.94; S, 6.66

Lipophilic

Hydrophilic
STATINS

- Competitive inhibitors of HMG CoA reductase (rate-limiting step in cholesterol biosynthesis)
- Most powerful drugs for lowering LDL-cholesterol (LDL-C) **30-63%** reductions
- Treatment of hypercholesterolemia and mixed hyperlipidemia
- Primary and secondary prevention of CV diseases
- Clinical benefits of lipid lowering: as little as 6 mo. (before significant regression of atherosclerosis occurs).
- Other factors must contribute:
  - Plaque stabilization
  - Reversal of endothelial dysfunction
  - Decreased thrombogenicity
Statins and cholesterol synthesis

- Max on LDL-C
- Min HDL-C increase
- TG decrease 20-40%
- Decrease in VLDL synthesis and to clearance of VLDL remnant particles by apo B/E (LDL) receptors.
Additive hypolipidemic effect when any of the statins is used in combination with a bile acid sequestrant or the cholesterol absorption inhibitor ezetimibe.
Dose-dependent effects of ATOR on TG and LDL VLDL in pts with hyperlipemia

Initial TG: 600 mg/dl
Initial LDL-C 119 mg/dl

Bakker-Arkema et al JAMA 1996
Side effects

- **Hepatic dysfunction**
- Muscle injury
- Renal dysfunction
- Behavioral and cognitive
- Cancer
- Diabetes mellitus
- Other
- Risks in pregnancy
## Dose, side effects, and drug interactions of lipid lowering drugs: Statins

<table>
<thead>
<tr>
<th>Drug class (HMG CoA reductase inhibitors)</th>
<th>Dose</th>
<th>Dosing</th>
<th>Major side effects and drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>20-80 mg/day</td>
<td>Take with evening meal. BID if dose &gt;20 mg/day.</td>
<td>Headache; nausea; sleep disturbance; Elevations in hepatocellular enzymes and alkaline phosphatase.</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10-80 mg/day</td>
<td>Take at bedtime.</td>
<td>Myositis and rhabdomyolysis, primarily when given with gemfibrozil or cyclosporine; myositis is also seen with severe renal insufficiency (CrCl &lt;30 mL/min).</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>5-80 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20-80 mg/day</td>
<td>BID if dose &gt;40 mg/day.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80 mg SR/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10-80 mg/day</td>
<td></td>
<td>Lovastatin, atorvastatin, rosuvastatin, and simvastatin potentiate effect of warfarin and all but rosvastatin raise digoxin levels; these interactions not seen with pravastatin or fluvastatin.</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5-40 mg/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Statins and cholesterol synthesis

Elevations of transaminases may be the result of mevalonic acid depletion during the inhibition of cholesterol synthesis.

Hepatic dysfunction & statins

Risks associated with statin therapy: a systematic overview of randomized clinical trials. Kashani A et al., Circulation. 2006

- Risks of musculoskeletal, renal, and hepatic complications associated with therapy
- Period: 1996-2005
- 35 trials, 74,102 subjects (fup 1-65 mo.)
  - Absolute risk of transaminase elevations significantly higher with statins (RD, 4.2; 95% CI, 1.5 to 6.9).
  - not of myalgias, creatine kinase elevations, rhabdomyolysis, or withdrawal of therapy compared with placebo.
Incidence of Increase in Serum ALT Levels >3 Times the ULN Among Different Trials, by Statin Dose

<table>
<thead>
<tr>
<th>Reference (statin)</th>
<th>No. of patients</th>
<th>Incidence, % (No.) of patients</th>
<th>Placebo</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT² (pravastatin vs atorvastatin)</td>
<td>4162</td>
<td>NA</td>
<td></td>
<td>1.1</td>
<td>3.3</td>
<td></td>
<td>&lt;.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>HPS²⁸&lt;sup&gt;c&lt;/sup&gt; (simvastatin)</td>
<td>20,563</td>
<td>1.28 (131)</td>
<td>1.35 (139)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Newman et al²²&lt;sup&gt;d&lt;/sup&gt; (atorvastatin)</td>
<td>14,236</td>
<td>0.17 (3)</td>
<td>0.11 (8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXCEL²⁴&lt;sup&gt;e&lt;/sup&gt; (lovastatin)</td>
<td>8245</td>
<td>0.1 (2)</td>
<td>0.1 (2)</td>
<td>0.9 (11)</td>
<td>1.5 (20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JUPITER²⁵ (rosuvastatin)</td>
<td>17,802</td>
<td>0.2 (17)</td>
<td>0.3 (23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.34</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS³³ (lovastatin)</td>
<td>6490</td>
<td>0.3 (11)</td>
<td>0.6 (18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

No more than 3% of the studied patients’ sample
Even not significantly different from PLACEBO
Eventually, dose-dependent, similar for all statins
Most cases improve: adaptation or tolerance

Hepatic dysfunction & statins


- Large cohort study from England and Wales
- Similar risks of hepatic dysfunction with different statins
- Exception of a higher risk with **fluvastatin**
Hepatic dysfunction & statins
In the Primary care setting

- 1,014 patients taking statins
- 1% pts. transaminase elevations >3xUNL
- 0.5% transaminase elevations 2-3xUNL
- None related to statin use

Hepatic dysfunction & statins

Computerized records

- 23,000 patients taking statins
- 0.1% of patients (n=17) ALT >10x attributable to statins
- 13/17 cases associated with drug interactions

Hepatic dysfunction & statins Guidelines (I)

- FDA
  - Liver testing before and at 12 wks after initiation of statins
  - At any elevation of dose and periodically thereafter
  - **HOWEVER only expert opinion**
Hepatic dysfunction & statins
Guidelines (II)

- Routine monitoring of liver function necessary
  - identify and then monitor patients with preexisting liver disease
  - receiving concomitant medications with a potential for drug interactions

- Possibly changing medications or lowering the statin dose
  - in patients who are found to have an alanine aminotransferase (ALT) level >3xUNL confirmed on a second occasion

Weismantel, D. What laboratory monitoring is appropriate to detect adverse drug reactions in patients on cholesterol-lowering agents?. J Fam Pract 2001; 50:927
Drug-induced liver injury

- ALT >2xUNL ?
- ALT >3xUNL ?
- ALT >10xUNL (true hepatotoxicity)

- **Hy Rule criteria:**
  - ALT >3x + Tot. bilirubin >2x
  (at any time after starting a new drug)

Pravastatin at a low dose

If the LDL-C remains elevated

combined therapy with a bile acid sequestrant
The combination of a statin and a bile acid binding resin is more effective than either alone

CHRONIC LIVER DISEASE AND USE OF STATINS

1 Pts with baseline elevations in aminotransferases:

not at increased risk when prescribed a statin

CHRONIC LIVER DISEASE AND USE OF STATINS

Pts without evidence of alcohol abuse, hepatitis B, or C

Cohort 1: 342 (many of whom presumably had fatty liver or NASH), hyperlipidemia, AST >40 IU/L [mean 55 IU/L] or ALT >35 IU/L [mean 43 IU/L] prescribed statins

Cohort 2: 1,437 hyperlipidemic patients with normal transaminases prescribed a statin

Cohort 3: 2,245 patients with baseline aminotransferase elevation not prescribed a statin

individuals with elevated baseline liver enzymes do not have higher risk for hepatotoxicity from statins

6 months follow up

Chalasani et al Gastroenterology 2004
Effects of Statin Treatment on Serum Alanine Aminotransferase (ALT) Levels in Patients With Normal or Elevated Baseline ALT Levels

fluctuations in liver enzyme values may represent natural disease progression rather than a statin-related effect
**Efficacy and Safety of High-Dose Pravastatin in Hypercholesterolemic Patients with Well-Compensated Chronic Liver Disease: Results of a Prospective, Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial**

James H. Lewis, Mary Ellen Mortensen, Steven Zweig, Mary Jean Fusco, Jeffrey R. Medoff, and Rene Belder for the Pravastatin in Chronic Liver Disease Study Investigators

- mean LDL-C level >100 mg/dL
- TG level <400 mg/dL
- chronic, well-compensated liver disease (23% chronic hepatitis C, 65% NAFLD, or any other chronic liver disease)
- AST, ALT <5 UNL
- Exclusion of major liver, systemic diseases
- Effect on lipidemia
- Effect on ALT
  - normal baseline: up to ALT 2x
  - abnormal baseline: ALT 2x

**326 Subj**

**163 Prava 80 mg**

**163 Placebo**

**12, 36 wks**

Lewis et al, Hepatology 2007
### Table 6. Cumulative Incidence of Subjects Who Met the Primary Alanine Aminotransferase Safety Endpoint (for All Patient Diagnoses)

<table>
<thead>
<tr>
<th>Week</th>
<th>Pravastatin [n/N (%)]*</th>
<th>Placebo [n/N (%)]*</th>
<th>95% Confidence Interval†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0/160 (0%)</td>
<td>1/160 (0.6%)</td>
<td>−1.8, 0.6</td>
<td>0.2850</td>
</tr>
<tr>
<td>2</td>
<td>0/160 (0%)</td>
<td>2/160 (1.3%)</td>
<td>−3.0, 0.5</td>
<td>0.1490</td>
</tr>
<tr>
<td>4</td>
<td>2/160 (1.3%)</td>
<td>4/160 (2.5%)</td>
<td>−4.2, 1.7</td>
<td>0.3967</td>
</tr>
<tr>
<td>6</td>
<td>6/160 (3.8%)</td>
<td>7/160 (4.4%)</td>
<td>−5.0, 3.7</td>
<td>0.7369</td>
</tr>
<tr>
<td>8</td>
<td>6/160 (3.8%)</td>
<td>8/160 (5.0%)</td>
<td>−5.7, 3.2</td>
<td>0.5468</td>
</tr>
<tr>
<td>12</td>
<td>9/160 (5.6%)</td>
<td>11/160 (6.9%)</td>
<td>−6.6, 4.1</td>
<td>0.6095</td>
</tr>
<tr>
<td>16</td>
<td>9/160 (5.6%)</td>
<td>12/160 (7.5%)</td>
<td>−7.3, 3.5</td>
<td>0.4805</td>
</tr>
<tr>
<td>20</td>
<td>9/160 (5.6%)</td>
<td>15/160 (9.4%)</td>
<td>−9.5, 2.0</td>
<td>0.1897</td>
</tr>
<tr>
<td>24</td>
<td>9/160 (5.6%)</td>
<td>17/160 (10.6%)</td>
<td>−11.0, 1.0</td>
<td>0.0951</td>
</tr>
<tr>
<td>28</td>
<td>10/160 (6.3%)</td>
<td>18/160 (11.3%)</td>
<td>−11.2, 1.2</td>
<td>0.1048</td>
</tr>
<tr>
<td>32</td>
<td>10/160 (6.3%)</td>
<td>19/160 (11.9%)</td>
<td>−11.9, 0.6</td>
<td>0.0762</td>
</tr>
<tr>
<td>36</td>
<td>12/160 (7.5%)</td>
<td>20/160 (12.5%)</td>
<td>−11.6, 1.6</td>
<td>0.1379</td>
</tr>
</tbody>
</table>

NS
High-dose pravastatin daily to hypercholesterolemic subjects with chronic, well compensated liver disease: efficacious and safe.

Pravastatin significantly lowered TC, LDL-C, and TGs

Frequency of ALT elevations (doubled from normal or elevated baseline) N.S. prava vs. placebo

Lack of significant hepatotoxicity developing in patients with compensated chronic liver disease treated with a statin.

Hypercholesterolemic pts with compensated chronic active liver disease: should not be denied access to pravastatin (or similar agents) solely on the basis of their liver disease.
The prevalence and etiology of elevated aminotransferase levels

**Causes of hypertransaminasemia**
- A = autoimmune
- B = hep B
- C = hep C
- D = drugs
- E = ethanol (ALD)
- F = fatty
- G = growth (tumour)
- H = hemodinamics (congestive)
- I = iron, Wilson, alpha1AT def., celiac disease, hypothyroidism

**Asymptomatic hypertransaminasemia**
7.9% of the US population
- Most common etiologies:
  - NAFLD
  - hepatitis C
  - ALD
  - Hepatitis B
  - hemochromatosis

**Increased Visceral Adiposity**

- **POOR PHYSICAL EXERCISE**
- **DIET**
- **DRUGS XENOBIOTICS**
- **GENETIC VARIANTS**

- Striated muscle

**INSULIN RESISTANCE**

- **LIFE STYLES**
  - Overweight obesity

- **ADIPOCYTOKINES**
  - TNF-α, IL-6, IL-1 (+)

- **HORMONES**
  - LEPTIN (+)
  - RESISTIN (+)
  - ADIPONECTIN (-)

- **INTESTINAL MICROBIOTA**
  - Endotoxins
  - Endogenous ethanol

- Lipolysis
- Inflammation

- **↑ FFAs**

- **↑ TG synthesis**

- **↑ FFA β-oxidation**

- **↑ Oxidative stress**

- **↓ Antioxidant defences**

- **Hepatic Mitochondrial Dysfunction**

- **Free Oxygen Radicals**
  - CYP 2E1
  - PPARα-γ

- **Lipid Peroxidation**
  - Iron

- **Steatosis**

- **Steatohepatitis (NASH)**

- **Fibrosis Cirrhosis**

- **HCC**

- **Overweight OBESITY**

From: Krawczyk, Bonfrate, Portincasa, Best Pract Clin Gastroenterol 2010
• Statin treatment safe
• Can improve liver tests and reduce CV morbidity in pts with mild-to-moderately abnormal liver tests potentially attributable to NAFLD.
Dallas Heart Study

- relationships between statin use, ALT elevations, and hepatic steatosis
- Hepatic TG content measured
- Statin group vs no statin: NS

<table>
<thead>
<tr>
<th></th>
<th>Statin use</th>
<th>None</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis</td>
<td>40%</td>
<td>38%</td>
<td>0.89</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>13%</td>
<td>15%</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Statins and viral hepatitis C: beneficial effects?

- On HCV-associated dysmetabolic syndrome and increased CV risk? (IR, steatosis, hypocholesterolemia) (Lonardo et al, 2008)

- Statins safe but also beneficial in these patients as a potential adjuvant therapy for HCV infection (Bader et al Am J Gastro 2008; Ye et al, PNAS 2003; Henderson et al DDS 2010)
Statins and viral hepatitis C: no effect on transaminasemia

- Prevalence in USA 1.6%
- Chronic condition, often found in high risk CVD pts
- **Stanford Veterans Administration Hospital Study:**
  - HCV(+) and increased transaminases±statins vs HCV(-) no statins
  - No different of mild-moderate (P=.94) to severe (P=.87) increases in liver enzyme levels between statin-treated groups ±HCV infection

Statin therapy and serum transaminases among a cohort of HCV-infected veterans

- Effect of statin therapy on serum AST and ALT levels in a 20 HCV-infected veterans
- Follow up 6-12 mo.
- Matched (age, stage of fibrosis, and time between HCV diagnosis and statin start dates) with up to four HCV-infected patients who did not use statins

Patients on statins:
- higher median BMIs
- more likely to have diabetes
- higher total cholesterol levels
- Higher baseline ALT

Decreased transaminases in HCV-infected patients taking statins

Henderson et al, DDS 2010
PBC and Cholesterol-lowering agents

- Statins
  - **Simva**: 10mg/d x 2 mo + UDCA 10-15 mg/bw (lipidemia[-], cholestasis [-])(1, 2)
  - Prava idem (3)
  - **Ator** (4)
- UDCA (long-term effect on HMGCoA)
  - UDCA > SIMVA (5)
- Cholestyramine (?)[pruritus]
- **Fibrates** (lipidemia[-], cholestasis [-]?)

PBC & Cholesterol metabolism

Increased CV risk?

(Danger: statin accumulation at toxic levels)

STATINS

LDL receptors
LDL clearance
Chol synthesis
BS synthesis
BS secretion
Micellization
Chol absorption

Injury
Cholestasis

LP-X* LDL-C

*anti-atherogenic properties

LCAT, lecithin:cholesterol acyltransferase

Sorokin et al, Atherosclerosis 2007
### PBC & Studies on CV events

<table>
<thead>
<tr>
<th>Author's name with reference numbers</th>
<th>Name of the study</th>
<th>Number of patients</th>
<th>Patients characteristics according to Scheuer staging of PBC</th>
<th>Follow-up period</th>
<th>Outcome measures</th>
<th>Statistical results</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longo [26]</td>
<td>Italian prospective observational study</td>
<td>400</td>
<td>188 patients with symptoms, 152 patients with liver cirrhosis</td>
<td>6.2 years</td>
<td>Fatal and non-fatal MI and CVE</td>
<td>Total cholesterol: 200–250 mg/dl, HR = 1.14; 250–300 mg/dl, HR = 3.85; &gt;300 mg/dl, HR = 2.41</td>
<td>0.873, 0.073, 0.262</td>
</tr>
<tr>
<td>Crippin [27]</td>
<td>Mayo prospective observational study</td>
<td>312</td>
<td>Stage I (16), stage II (67), stage III (120), stage IV (109)</td>
<td>7.4 years</td>
<td>Fatal and non-fatal MI, CVE</td>
<td>Number of observed deaths = 7 vs. expected per US census = 4</td>
<td>0.17</td>
</tr>
<tr>
<td>Van Dam [28]</td>
<td>Dutch retrospective survey</td>
<td>596</td>
<td>All stages included, otherwise not specified</td>
<td>Retrospective database query from 1979 to 1992</td>
<td>Fatal and non-fatal MI, CVE</td>
<td>Standardized mortality ratio = 0.8</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; CVE, cerebrovascular events; ↓, decrease; ↑, increase.
Simvastatin in primary biliary cirrhosis: effects on serum lipids and distinct disease markers
Ritzel et al J Hepatol 2002

Serum markers of cholestasis and serum immunoglobulins in patients with PBC before and during treatment with HMG-CoA reductase inhibitor simvastatin

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>18 (8–39)</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>28 (11–88)</td>
</tr>
<tr>
<td>ALP (U/l)</td>
<td>323 (124–706)</td>
</tr>
<tr>
<td>GGT (U/l)</td>
<td>128 (27–384)</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>0.5 (0.2–0.9)</td>
</tr>
<tr>
<td>IgA (g/l)</td>
<td>3.4 (1.9–5.5)</td>
</tr>
<tr>
<td>IgG (g/l)</td>
<td>20.7 (15.5–33.8)</td>
</tr>
<tr>
<td>IgM (g/l)</td>
<td>5.6 (4.2–8.5)</td>
</tr>
</tbody>
</table>

* The observational period lasted 2 months. Values are median (range).

*P < 0.05 vs. baseline (before treatment).
Statins and cholestasis (PBC)

- 15 Pts early PBC
- Incomplete biochem. response to UDCA
- **atorvastatin** 10 -> 20 -> 40 mg/day x 4 wks each
- Total-C and LDL-C decreased by 35% and 49%, respectively
- **Cholestasis not improved**
- Significant transaminase elevations common

Stojakovic et al, Hepatology 2007
## Fibrates intervention trials in the treatment of PBC

<table>
<thead>
<tr>
<th>Stage of the PBC in Scheuer’s classification</th>
<th>Control group</th>
<th>Intervention group</th>
<th>Study design</th>
<th>Mean ∆ in ALP U/l in fibrate group</th>
<th>Mean ∆ in AST U/l in fibrate group</th>
<th>Mean ∆ in ALT U/l in fibrate group</th>
<th>Mean ∆ in IgM mg/dl in fibrate group</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 stage I, 9 stage II, 3 stage III, 1 stage IV All stages, but otherwise not specified</td>
<td>UDCA 600 mg/day, 7 patients</td>
<td>16 patients, bezafibrate 400 mg/day, UDCA 600 mg/day</td>
<td>Randomized cross-over prospective study 12 months</td>
<td>↓171</td>
<td>↑1</td>
<td>↓7</td>
<td>↓53</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>4 stage I, 3 stage II</td>
<td>None</td>
<td>10 patients, bezafibrate 400 mg/day + UDCA 600 mg/day, 7 patients, fenofibrate 150–200 mg/day</td>
<td>Prospective observational study 1 month</td>
<td>↓423</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Not specified</td>
<td>None</td>
<td>Bezaflibrate 400 mg/day, 3 patients, fenofibrate 150 mg/day, 2 patients</td>
<td>Prospective observational study 6 months</td>
<td>↓103</td>
<td></td>
<td>↓232</td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>5 stage I, 5 stage II, 2 stage III, 1 stage IV Not specified</td>
<td>None</td>
<td>13 patients, bezafibrate 400 mg/day, UDCA 600 mg/day</td>
<td>Prospective observational study 37.5 months</td>
<td>↓265</td>
<td></td>
<td>↓156</td>
<td></td>
<td>&lt;0.055</td>
</tr>
<tr>
<td>Not specified</td>
<td>None</td>
<td>Fenofibrate 100 mg/day, 4 patients, fenofibrate 150 mg/day, 5 patients, UDCA 600 mg/day</td>
<td>Prospective observational study 6 months</td>
<td>↓99</td>
<td>↑17</td>
<td>↓17.3</td>
<td>↓63</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Not specified</td>
<td>11 patients, UDCA 600 mg/day</td>
<td>11 patients, bezafibrate 400 mg/day, UDCA 600 mg/day</td>
<td>Prospective randomized study 6 months</td>
<td>↓220</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>5 stage I, 2 stage II, 2 stage III, 1 stage IV</td>
<td>None</td>
<td>10 patients, bezafibrate 400 mg/day, UDCA 600 mg/day</td>
<td>Prospective observational study 1 month</td>
<td>↓170</td>
<td>↓7</td>
<td>↓20</td>
<td></td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

IgM, immunoglobulin M; ∆, change; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ↓, decrease; ↑, increase.
Fibrates in PBC: putative mechanisms

- Lipid-lowering effect
- Anti-inflammatory pathways
  - activation of peroxysome proliferator-activated receptor
  - expression of multiple drug resistance gene-3
  - amelioration of hepatobiliary inflammation in PBC
    (Dohmen et al WJG 2004)

- One pilot study: histopathological improvement in PBC pts. on long-term bezafibrate monotherapy 200 mg/b.i.d (Kurihara et al Am J Gastro 2002)
Statins and alcohol intake

- Poorly studied
- Heart Protection Study:
  - Pts >21g ETOH intake/wk
  - No evidence of a higher risk of statin-related myopathy or elevation in liver enzyme levels


Statins and diabetic liver disease

- Large cohort of diabetic patients (1303 vs. 5212 controls)
- Statin use associated with a significant reduction in the risk of HCC among patients with diabetes
  - Inhibition of downstream products of the mevalonate pathway (activator of cellular proteins, including K-ras 4)
  - Inhibition of proteosome pathway (limiting the breakdown of both p21 and p27: growth-inhibitory effects)

Statins and post-liver transplant

- Dyslipidemia observed in 20% to 60% of cases
- Immunosuppression: hypercholesterolemia
- Tacrolimus and cyclosporine A metabolized via CP450 system: potential adverse effects with statins
- Less with PRAVA

- 6 wks PRAVA or CERI well tolerated
- Long-term effects missing


Algorithm for management of abnormal liver enzymes before and during statin treatment.

Gallstone phenotypes

Portincasa, Moschetta, Palasciano, The Lancet 2006
Rapid Phase Transition
Anhydrous cholesterol crystals
Monohydrate cholesterol crystals
Precipitation, aggregation

Intestine
High cholesterol absorption
Hypomotility
Anaerobic microflora
High hydrophobic bile salt absorption

Visceral adiposity & inflammation
Insulin resistance
Metabolic syndrome

Liver
Hypercholesterobilia

Genetic factors and LITH genes

Gallbladder
Rapid Phase Transition
Anhydrous cholesterol crystals
Monohydrate cholesterol crystals
Precipitation, aggregation

Dysmotility
Leiomiopathy
Inflammation
Mucin accumulation

Cholesterol Gallstones

Portincasa et al. Sem Liv Dis 2011 (in press)
Secretion of lipids in bile (Step 1)

Hepatocyte

**Biosynthesis**
- Acetate
- HMGCR
- CMR
- SR-BI

**Uptake**
- HDL

**Storage**
- Cholesteryl Esters
- ACAT

**Esterification**
- Esterification

**Catabolism**
- CYP7A1
- CYP27
- “α”

**Efflux**
- ABCA1
- VLDL

**Basolateral Membrane**
- ABCG5/G8
- ABCB11
- ABCB4
- MDR3
- BSEP
- FXR
- NR1H3
- RXR

**Canalicular Lumen**
- LXR
- “γ”

**Canalicular Membrane**
- PL

Adapted from Portincasa P. Biliary lithiasis. Basic science, current diagnostic and therapeutic approaches, Springer 2008
Cholesterol Secretion

Biliary Chol supersaturation

Cholesterol Crystallization

Gallstone Formation
Typical crystals of monohydrate cholesterol in bile

Refrangent microscopy

RAPID PHASE TRANSITION
Statins and Gallstones

- Decreased risk of gallstone disease requiring cholecystectomy?
- Case-control study
- 27,035 GSD patients requiring cholecystectomy to 106,531 matched controls
- Long-term statin use (>20 prescriptions filled):
  - decreased risk of GSD requiring cholecystectomy (adjusted OR 0.64).
  - protective effect 1 to 1.5 years of statin use.

Bodmer M et al. JAMA 2009
Statins-Cholesty and Gallstones

8 hypercholesterolemic pts → Simva 20mg/d → Cholesty 4gx2/d → Combined

4 wks

Lipidemia, Motility, bile composition

**TABLE I** Serum lipid concentrations in eight patients with primary hypercholesterolaemia, treated for four weeks with simvastatin and cholestyramine, alone or in combination

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Simvastatin (20 mg/day)</th>
<th>Cholestyramine (8 g/day)</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total-cholesterol (mmol/l)</td>
<td>8·1 (0·2)</td>
<td>5·7 (0·3)*</td>
<td>7·4 (0·2)†</td>
<td>5·5 (0·2)*</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1·3 (0·1)</td>
<td>1·5 (0·1)†</td>
<td>1·5 (0·1)†</td>
<td>1·5 (0·1)†</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>5·9 (0·3)</td>
<td>3·1 (0·3)*</td>
<td>4·4 (0·3)*</td>
<td>2·9 (0·1)*</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2·1 (0·3)</td>
<td>2·5 (0·8)</td>
<td>3·3 (0·7)†</td>
<td>2·3 (0·6)</td>
</tr>
</tbody>
</table>

*p<0·01 v baseline; †p<0·05 v baseline. Data shown as mean (SEM).

**TABLE II** Biliary lipid composition in eight patients with primary hypercholesterolaemia, treated for four weeks with simvastatin and cholestyramine, alone or in combination

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Simvastatin (20 mg/day)</th>
<th>Cholestyramine (8 g/day)</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSI</td>
<td>0·99 (0·08)</td>
<td>1·00 (0·08)</td>
<td>1·03 (0·15)</td>
<td>0·93 (0·14)</td>
</tr>
<tr>
<td>Molar percentages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>5·8 (0·6)</td>
<td>6·0 (0·6)</td>
<td>5·8 (0·8)</td>
<td>6·3 (1·1)</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>16·4 (1·3)</td>
<td>16·6 (0·9)</td>
<td>15·7 (1·2)</td>
<td>21·2 (2·4)*</td>
</tr>
<tr>
<td>Bile salts</td>
<td>77·8 (1·7)</td>
<td>77·4 (1·4)</td>
<td>78·5 (1·4)</td>
<td>72·5 (2·9)*</td>
</tr>
</tbody>
</table>

*p<0·05 v baseline. Data shown as mean (SEM).
### TABLE III  Bile salt composition in eight patients with primary hypercholesterolaemia, treated for four weeks with simvastatin and cholestyramine, alone or in combination

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Simvastatin (20 mg/day)</th>
<th>Cholestyramine (8 g/day)</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tauroursodeoxycholate (%</td>
<td>0.49 (0.16)</td>
<td>0.50 (0.16)</td>
<td>0.08 (0.03)</td>
<td>0.10 (0.05)</td>
</tr>
<tr>
<td>Glycoursodeoxycholate</td>
<td>1.91 (0.58)</td>
<td>2.06 (0.50)</td>
<td>0.65 (0.24)</td>
<td>0.56 (0.25)</td>
</tr>
<tr>
<td>Taurocholate</td>
<td>9.67 (0.96)</td>
<td>10.40 (0.91)</td>
<td>10.07 (1.16)</td>
<td>10.47 (2.14)</td>
</tr>
<tr>
<td>Glycocholate</td>
<td>28.23 (2.23)</td>
<td>27.64 (1.88)</td>
<td>59.37 (3.93)*</td>
<td>55.55 (2.43)*</td>
</tr>
<tr>
<td>Taurochenoxycholate</td>
<td>9.16 (1.06)</td>
<td>9.90 (1.14)</td>
<td>2.77 (0.79)</td>
<td>3.52 (0.46)*</td>
</tr>
<tr>
<td>Taurodeoxycholate</td>
<td>4.69 (1.05)</td>
<td>5.13 (0.89)</td>
<td>0.88 (0.33)</td>
<td>1.50 (0.26)†</td>
</tr>
<tr>
<td>Glycocholenoxycholate</td>
<td>27.41 (2.2)</td>
<td>26.17 (2.58)</td>
<td>19.33 (1.89)</td>
<td>19.37 (1.34)†</td>
</tr>
<tr>
<td>Glycodeoxycholate</td>
<td>18.44 (2.73)</td>
<td>18.20 (2.48)</td>
<td>6.85 (1.89)</td>
<td>8.93 (1.68)‡</td>
</tr>
<tr>
<td>Hydrophobicity index</td>
<td>0.34 (0.01)</td>
<td>0.33 (0.01)</td>
<td>0.19 (0.02)†</td>
<td>0.22 (0.01)*</td>
</tr>
<tr>
<td>Taurine/glycine conjugated bile salts</td>
<td>0.33 (0.05)</td>
<td>0.36 (0.05)</td>
<td>0.16 (0.04)†</td>
<td>0.19 (0.04)†</td>
</tr>
</tbody>
</table>

*p<0.001 v baseline; †p<0.01 v baseline; ‡p<0.05 v baseline; §see text.
Data shown as mean (SEM).

### TABLE IV  Postprandial gall bladder motility in eight patients with primary hypercholesterolaemia, treated for four weeks with simvastatin and cholestyramine, alone or in combination

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Simvastatin (20 mg/day)</th>
<th>Cholestyramine (8 g/day)</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting volume (V_{0}) (ml)</td>
<td>23.2 (2.3)</td>
<td>28.7 (2.8)*</td>
<td>23.4 (4.2)</td>
<td>26.0 (4.9)</td>
</tr>
<tr>
<td>Minimal volume (V_{\text{min}}) (ml)</td>
<td>5.9 (0.7)</td>
<td>5.7 (0.9)</td>
<td>8.9 (2.4)</td>
<td>9.5 (2.3)</td>
</tr>
<tr>
<td>Maximal decrease (%)</td>
<td>73 (3)</td>
<td>81 (2)†</td>
<td>66 (3)</td>
<td>65 (4)</td>
</tr>
<tr>
<td>Maximal decrease (ml)</td>
<td>17.3 (2.2)</td>
<td>23.0 (2.3)*</td>
<td>14.5 (1.9)</td>
<td>16.6 (2.9)</td>
</tr>
</tbody>
</table>

*p<0.01 v baseline; †p<0.05 v baseline. Data shown as mean (SEM).
# Dose, side effects, and drug interactions of lipid lowering drugs: Others

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Dose</th>
<th>Dosing</th>
<th>Major side effects and drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemfibrozil</td>
<td>600 mg BID</td>
<td>30 to 60 min before meals.</td>
<td>Potentiates warfarin action. Absorption of gemfibrozil diminished by bile acid sequestrants.</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Nanocrystal 145 mg/day Micronized 160-200 mg/day</td>
<td>Micronized taken with meals. Use lower doses with renal insufficiency.</td>
<td>Skin rash, gastrointestinal (nausea, bloating, cramping) myalgia; lowers blood cyclosporine levels; potentially nephrotoxic in cyclosporine treated patients. Avoid in patients with CrCr &lt;30 mL/min.</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>1-12 g/day</td>
<td>Given with meals. Start with 100 mg BID and titrate to 500 mg TID. After 6 weeks, check lipids, glucose, liver function, and uric acid. Increase dose as needed.</td>
<td>Prostaglandin-mediated cutaneous flushing, headache, warm sensation, and pruritus; hyperpigmentation (particularly in intertriginous regions); acanthosis nigricans; dry skin; nausea; vomiting; diarrhea; and myositis.</td>
</tr>
<tr>
<td><strong>Bile acid sequestrants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>4-24 g/day</td>
<td>Take within 30 min of a meal. A double dose with dinner produces same lipid-lowering effect as BID dosing.</td>
<td>Nausea, bloating, cramping, and constipation; <strong>elevations in hepatic transaminases and alkaline phophatase.</strong> Impaired absorption of fat soluble vitamins, digoxin, warfarin, thiazides, β-blockers, thyroxine, and phenobarbital.</td>
</tr>
<tr>
<td>Colestipol</td>
<td>5-30 g/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colesevelam</td>
<td>3.75 g/day</td>
<td>Take with meals QD or divided BID</td>
<td>Similar</td>
</tr>
<tr>
<td><strong>Cholesterol absorption inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>10 mg/day</td>
<td></td>
<td><strong>Increased transaminases in combination with statins</strong></td>
</tr>
<tr>
<td>Neomycin</td>
<td>1 g BID</td>
<td></td>
<td>Ototoxicity; nephrotoxicity</td>
</tr>
<tr>
<td>Probucol</td>
<td>500 mg BID</td>
<td></td>
<td>Loose stools; eosinophilia; QT prolongation; angioneurotic edema.</td>
</tr>
</tbody>
</table>
EZETIMIBE
new class of 2-azetidinones

(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one

(C24H21F2NO3)
m.w. 409.43
The small intestine provides dietary and reabsorbed biliary cholesterol to the body

Prevention of Cholesterol Gallstones by Inhibiting Intestinal XOL absorption

The small intestine provides dietary and reabsorbed biliary cholesterol to the body.
Effect of Ezetimibe on the Prevention and Dissolution of Cholesterol Gallstones

WANG, PORTINCASA, MENDEZ–SANCHEZ, URIBE, WANG
Gastroenterol., 2008
Gross morphology of livers

Ezetimibe (µg/day)

0 200
<table>
<thead>
<tr>
<th>Chow</th>
<th>High fat and high cholesterol</th>
<th>Ezetimibe (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>200</td>
</tr>
</tbody>
</table>

Liver Histology
COORDINATE REGULATION OF GALLBLADDER MOTOR FUNCTION IN THE GUT-LIVER AXIS

Prokinetic Effects of Cholestyramine

Palasciano, Portincasa et al, Gastro 1992

GS pts. (n=36)

Portincasa et al, Am J Gastro 1994

Portincasa et al, EJCI 1995
Cholestyramine as GB prokinetic agent in fasting: motilin or CCK?

Portincasa et al., Neurogastr & Motil 2000
CONCLUSIONS

• Several lipid-lowering drugs (LLDs) available
• Statins alone or in combination
• The problem of LLDs-induced liver damage
  • - transaminitis
  • - more severe damage
• The problem of an already existing liver damage
• Additional effects of LLDs on hepatobiliary tract
• Priority health problem: hyper-dyslipidemia and CV risk (I, II prevention)