Statins and Liver Disease

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Clinical Question

- A 55 yowm presents to your office for annual check up. He is obese, otherwise healthy. Father died of MI at age 61. Patient drinks "a 6 pack" on the weekends. His cholesterol is 280. LDL of 170. AST= 80, ALT = 45, T Bili= 0.3. You are discussing statin therapy.

  - A. You plan on starting lipitor only if his LFT's normalize off of EtOH.
  - B. You will offer him a statin now with recheck of LFT's in 6 weeks and recommend EtOH cessation.
  - C. You advise him to continue EtOH at "1 glass of wine an evening" and begin aggressive exercise program.
  - D. You refer him for a virtual colonoscopy because his chance of dieing from CRC far exceeds that as from CHD.

Overview

- **Statins and Cardiovascular Disease**
- **Review of Statins**
- Review of Fibrates (Tricor)
- Review of Niacin
- Review of cholesterol binding resins
- Review of other drug related liver diseases
- NAFLD and cholesterol-lowering drugs

CHD and Statins

- Coronary heart disease is number 1 killer in the USA
  - 1 out of 5 deaths
  - Stroke is the number 3 killer
    - 1 out of 15 deaths
- Statin use reduced coronary heart disease by 20-40%
  - Primary prevention reduced first MI by 37%
  - Reduces stroke risk by 30%
  - Reduces all cause death by 25-30%

Statins

- Lovastin - *Mevacor*
- Simvastatin – *Zocor*
- Pravastatin – *Pravachol*
- Fluvastatin – *Lescol*
- Atorvastatin – *Lipitor*
- Cerivastatin – *Baycol*
- Rosuvastatin – *Crestor*

Lovastatin/*Mevacor*

Lovastatin *Mevacor*

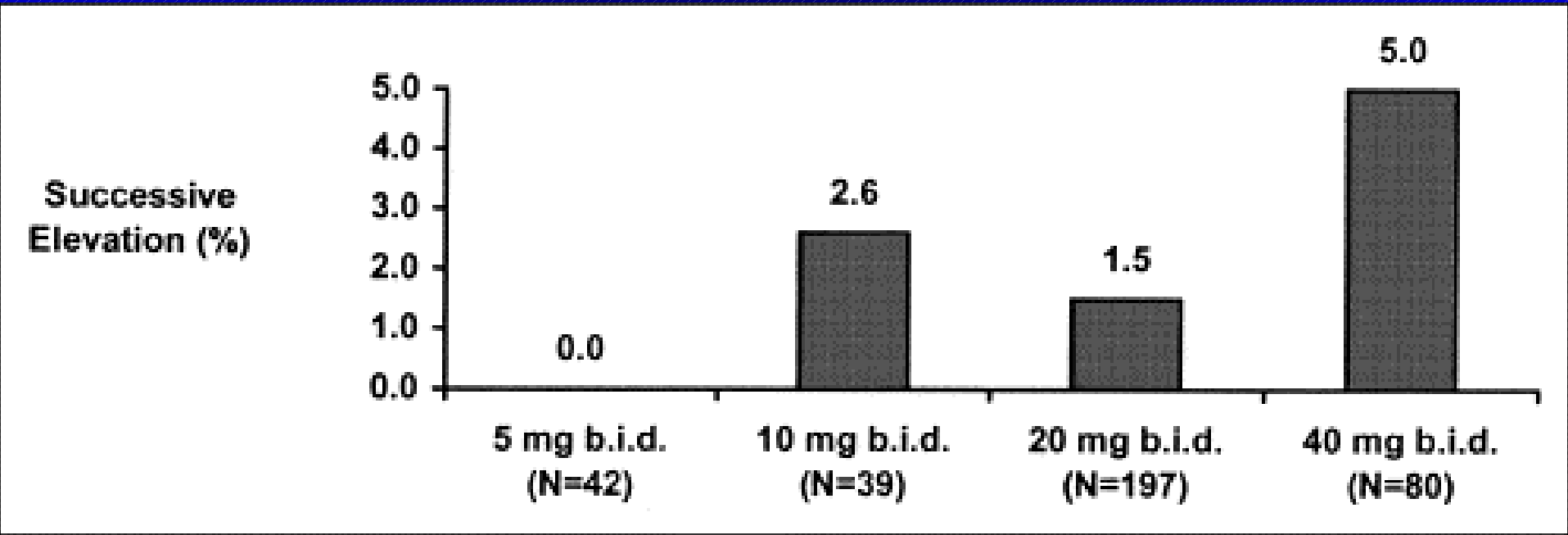
- Isolated from *Aspergillus terreus* 1982
- **1987**- received FDA accelerated approval
  - Toxicology Studies abnormal
  - "Liver function tests be performed before initiation of treatment, at 6 and 12 weeks after initiation of treatment or elevation in dose, and periodically thereafter. Should an increase in AST or ALT of 3 times the ULN or greater persist, withdrawal of therapy with Mevacor is recommended"

Lovastatin

- Toxicology studies
  - Rabbits (lower baseline HMG-CoA)
    - 100-200 mg/kg/day- hepatic necrosis
      - (800-2000 mg dose in humans)
      - Usual dose is 20-40 mg a day
    - Injury could be prevented with better nutrition/mevalonic acid
  - Dogs
    - Slight elevations in ALT without histologic damage

Lovastatin

- Premarketing clinical trials
  - 21% mild ALT increases
  - 1.9% >3 x ULN ALT:

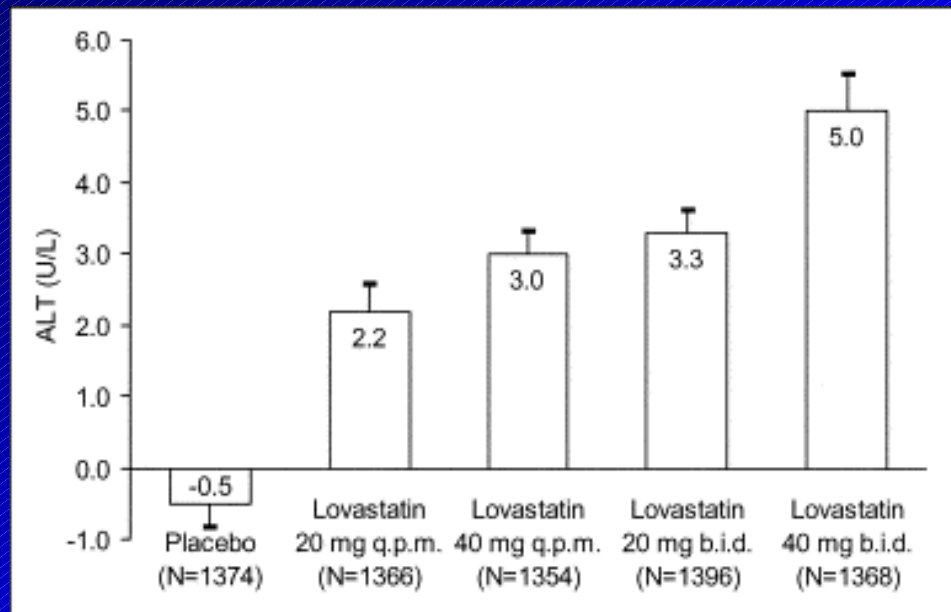


Lovastatin

- Pre-marketing Safety N = 2,045
- Drug discontinued per protocol if >3 x ULN in 15 (0.7%)
  - Rechallenge results
    - 7- recurrence of elevation = drug related
    - 3- probably drug-related
    - 3- alternative explanations
    - 2- negative rechallenge
      - Of the 10 drug related/probably drug related
        - » 5 baseline ALT elevations
        - » 7 regular ETOH use, 3 recent E-mycin

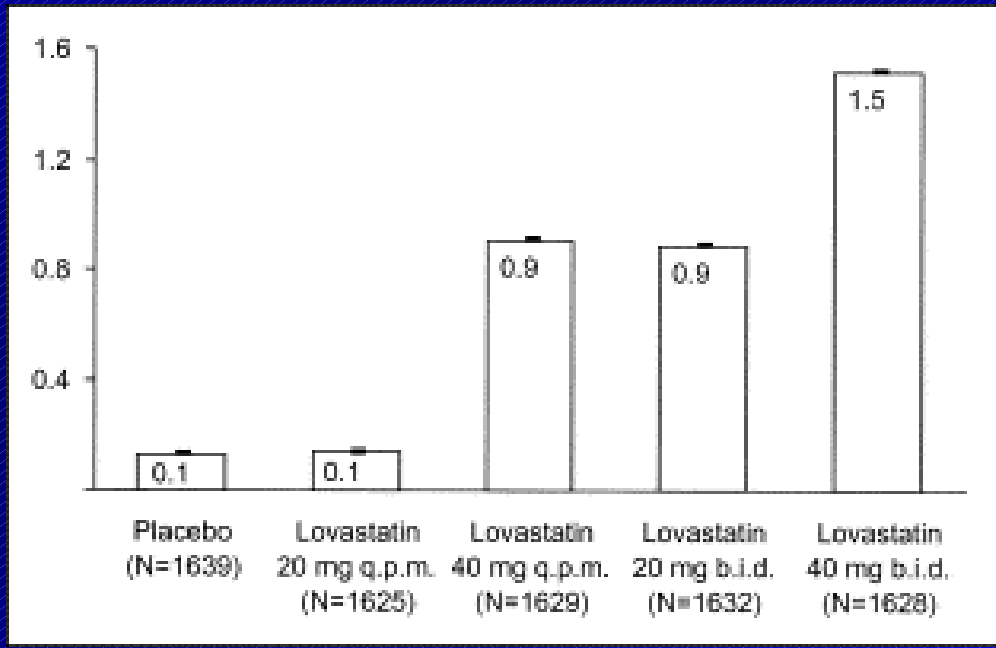
Lovastatin

- Post-marketing- Phase IV
- EXCEL- Expanded Clinical Evaluation of Lovastatin
  - N = 8,245
  - Double-blind placebo-controlled with mod-severe hypercholesterolemia
    - No prior LFT elevations
    - LFT's checked Q 6 week
    - Any ALT elevation



Lovastatin

- ALT > 3 x ULN
- 4/45 were symptomatic
  - Nausea, anorexia, fatigue
  - All in 80 mg/day group
  - 7 had elevated alk phos
  - 1 had elevated T Bili
  - Risk factors present
    - Daily ETOH, obesity, baseline ALT elevation, increased dose of Lovastatin



Lovastatin

- AFCAPS/TexCAPS-Air Force/Texas Coronary Arteriosclerosis Prevention Study
  - N = 6,605
  - Lovastatin 20 mg vs. placebo x 5 years
    - Week 18- 1,657 increased to 40 mg
    - LFT's at initiation, Q 6 wk x 1 year, Q 6 month
    - Exclusion LFT's >1.2 ULN, 50% over IBW, IDDM
  - Results
    - Elevation LFT's >3 x ULN
      - 18 (0.6%) Lovastatin vs. 11 (0.34%) Placebo
      - 14 normalized on treatment or had negative rechallenge
        - » 3 other causes
    - 127 had levels 2-3 x ULN, 72% decreased to <2 x ULN

Lovastatin

- AFCAPS/TexCAPS, cont.
  - Patients with baseline elevated LFT's
    - 136 Lovastatin vs. 130 Placebo
    - Of those ultimately 3 x ULN-
      - 1.1% had baseline elevation vs. 0.4% had baseline normal LFT's
      - Most with baseline elevations probably had NASH
    - Persistent elevation >3 X ULN
      - 2/136 Lovastatin vs. 1/130 Placebo

Lovastatin

- WAES- Worldwide Adverse Experience Database
  - 17 cases **"ALF"- Acute Liver Failure**
    - 1 metastatic disease to liver
    - 2 Autoimmune hepatitis
    - 1 Decompensated PBC
    - 2 minor LFT elevation- death other cause
    - 1 Lupus
    - 1 friend of a friend with no documentation
    - 1 inquiry whether lovastatin could cause ALF
    - 2 "quit functioning" livers
  - 9 cases including AIH- possible related
  - 1 in 2.67 million patient-treatment years (equal to idiopathic Acute Liver Failure)

Lovastatin

- WAES, cont.
  - **Acute hepatitis**
    - 232 cases
    - Liver bx available 60
      - 37 hepatitis, 7 acute hepatitis, 8 chronic active/persistent
      - 5 chemical
      - 3 autoimmune
      - 8 granulomatous
      - 4 inflammation
      - 7 cholestatic
      - 8 fatty liver
      - 2 cirrhosis
      - 5 cholangitis
      - 25 other
    - 38 probably/possibly drug related, 16 not, 13 unknown
    - All patients fully recovered

Lovastatin

- Drug-interactions
  - Metabolized by cytochrome P_{450}3A4
  - Concomitant inhibitor of **CYP3A4**
    - Erythromycin- associated with Multi organ failure
    - Other macrolide antibiotics- clarithromycin, azithromycin
    - Azole antibiotics- sulfamethoxazole, metronidazole
    - Cimetidine
    - Diltiazem
    - Estradiol/Estrogens
    - Quinidine
    - Grapefruit juice (200 mg for intestinal CYP3A4 irreversible inhibition, 1 liter for hepatic CYP3A4 inhibition)

Lovastatin

- Case reports
  - Anicteric Hepatitis
    - 57 yo female 9 months
    - 59 yo female 3 years
  - Acute Cholestatic Hepatitis
    - 58 yo man 3 years
    - 54 yo woman 2 months
  - All with biopsy proven disease
  - All fully recovered with drug discontinuation

Simvastatin/*Zocor*

Simvastatin/*Zocor*

- SSSS- Scandinavian Simvastatin Survival Study
  - Safety analysis 4444 x 5.4 years
    - Elevated LFT's and hepatitis
      - 1.8% simvastatin vs. 1.4% placebo
      - All fully recovered
  - Italian study 100 simvastatin vs. 90 pravastatin
    - 5% vs. 4.5% 3 x ULN within 6 months

Simvastatin/*Zocor*

- Heart Protection Study (HPS)
  - N = 20,536
  - 40 mg vs. Placebo x 5 years
    - LFT's 4 x ULN = 9 (0.09%) vs. 4 (0.04%)
    - All fully recovered

Simvastatin/*Zocor*

- Case reports (metabolized by CYP3A4)
  - Simvastatin x 3 years, addition of diltiazem
    - Rhabdomyolysis and acute hepatitis
  - 68 yof with DM, hypercholesterolemia, self-resumed troglitazone
    - Acute and severe hepatitis
    - Felt to be troglitazone mitochondrial toxicity
    - Myositis resolved, liver to cirrhosis in 12 weeks
  - Elderly woman with simvastatin and chlorzoxazone (CYP2E1) (Paraflex)
    - Cholestatic hepatitis
    - Resolved with drug withdrawal
  - 10 Case reports of acute hepatitis and elevated LFT's
    - 4/10 Biopsy confirmed
    - All resolved with medication discontinuation

Atorvastatin/*Lipitor*

Atorvastatin/*Lipitor*

- Pooled data published 1998 (Metabolized by CYP3A4)
  - 1845 patient-years of exposure
    - 1253 (50%) had 12 months plus
    - Withdrawal
      - Nausea, pain, depression, myalgia, pain, abnormal LFT's
      - 0.3%- not dose- dependent
      - 30 patients with ALT x 3 ULN- only 11 (<0.3%) stopped
      - Rate similar to placebo
- Pooled data published 2006
  - 14,236 patients
    - 10mg vs. 80mg vs. placebo
    - LFT's 3 x ULN= 0.1% x 0.6% x 0.2%

Atorvastatin/*Lipitor*

- 2001 MIRACL
  - N = 1072
  - 12 week check elevated LFT's
    - 10 mg 0.2%
    - 80 mg 2.3%
- Case Reports
  - Female with SLE receiving cyclophosphamide, choloroquine, prednisone, atrovastatin, calcium
    - After 6th week- ALT 800, Tbili 8.2- normal INR
    - Viral causes eliminated
    - Atorvastatin discontinued- ALT and T Bili normalized in 5 weeks

Pravastatin/*Pravachol*

Pravastatin/*Pravachol*

- PPPP- Prospective Pravastatin Pooling Project
  - 112,000 person-years of exposure
    - ALT >3 x ULN
      - 1.4% pravastatin and 1.4% control
      - Gallbladder disease 1.9% vs. 2.1%
      - If pre-existing elevated LFT's
        - » 40.1% pravastatin vs. 38.5% placebo further elevations
      - No severe hepatotoxicity

Pravastatin/*Pravachol*

- Case Reports (Not metabolized by P450 system)
  - 57 yo male started on pravastatin 20 mg/day 7 weeks prior
    - Acute cholestatic hepatitis
    - Work up negative
    - Resolved 7 weeks after discontinuation

Pravastatin

- Pharmacokinetics
  - Not metabolized by P450 system
  - No significant change with other CYP3A4 inhibitors
    - Verapamil, itaconazole, ketoconazole, clarithromycin , erythomycin, cyclosporine
    - Grapefruit juice

Fluvastatin/*Lescol*

Fluvastatin/*Lescol*

- Synthetic HMG-CoA reductase inhibitor
  - Extensive first-pass metabolism
    - Metabolized by CYP2C9
  - No reports of hepatotoxicity
- 2002 JAMA
  - Only patients with baseline elevations had later elevations
    - 0.2% on 20 mg
    - 2.7% on 80 mg

Cervistatin/*Baycol*

Cervistatin/*Baycol*

- Approved 1997
  - 2001 study n = 1,263
    - LFT increase was dose-related
    - Recovered with drug discontinuation
  - 2001- Voluntarily withdrawn after 31 deaths from rhabdomyosis
    - 12 on combination with Gemfibrozil
    - No reports of hepatotoxicity

Rosuvastatin/*Crestor*

Rosuvastatin/*Crestor*

- Newest statin
  - Minimal metabolism by CYP2C9
    - 90% excreted in feces
  - Phase III studies
  - N = 516- atorvastin vs. rosuvastatin
    - Reduction in LDL 35% vs. 43%
    - Side effects same- no hepatoxicity
  - STELLAR trial
    - Rosuvastatin vs. simvastatin vs. pravastatin
    - N = 1123
    - No patients required dose reduction or discontinuation from LFTs
  - Used in cirrhotics- n = 6
    - Well tolerated

Rosuvastatin/*Crestor*

- ASTEROID study
  - JAMA 2006
  - 507 on high dose Crestor with IVUS exams
  - LFTs
    - > 3 x ULN- 9
    - > 3 x ULN more than once – 1 (0.2)
  - CKs
    - CK >5 x ULN- 6
    - CK >5 x ULN more than once – 1 (0.2)

Continuing…

- Statins and Cardiovascular Disease
- Review of Statins
- **Review of Fibrates (Tricor, Lopid)**
- Review of Niacin
- Review of cholesterol binding resins
- Review of other drug related liver diseases
- NAFLD and cholesterol-lowering drugs


RX
ABBOTT LABORATORIES
TA
TA* 54 mg
TC
TC* 160 mg
Tricor®
(fenofibrate tablets)

Fibrates

- Fenofibrate (*Tricor*)
- Gemfibrozil (*Lopid*)
  - GI side effects- 5%
  - H/A, loss of libido, dizziness, insomnia 3-4%
  - Rodent liver
    - Peroxisone proliferation
    - Hepatic carcinoma in high doses
  - Human liver
    - Increase AST and ALT- same as controls
    - Decrease alk phos, GGT, Bilirubin

Fibrates

- Case reports
  - 5 patients with chronic hepatitis
    - 4 with hypergammaglobulinemia, increased ANA
    - Liver biopsy- lympho-plasmacytic infiltration
    - Cirrhosis in 3 on presentation and 2 later
    - Discontinuation of drug-
      - 3 normalized LFT's
      - 2 required immunosuppresion for normalization
  - 1 patient with acute hepatitis and eosinophilia
    - Resolved with discontinuation
    - Recurred with rechallenge

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RX
KOS PHARMACEUTICALS, INC.
KOS
500
500 mg
KOS
750
750 mg
KOS
1000
1000 mg
Niaspan®
(niacin extended-release tablets)

Niacin

- Multiple side effects
  - Flushing and palpitations
  - Worse DM, PUD, gout, hepatitis
    - SR- less flushing and palpitations
  - Hepatotoxic
    - Elevated LFT's, steatosis, fulminant failure
  - 1992 Literature review of hepatotoxicity
    - 6 IR
    - 2 SR
    - 10 changed from IR to SR

Niacin

- Combination
  - 1994 double blind randomized (n = 74)
    - Fluvastatin vs. fluvastatin plus niacin
    - AST rise
      - 8.3% vs. 28.9%
      - None symptomatic or >3 x ULN
  - 2002 multicenter open-label (n = 814)
    - Niacin plus lovastain 40 mg
      - LFT's >3 x ULN 0.5%
      - 10% withdrew for flushing
  - With ETOH
    - 44 yo male presented with encephalopathy

Niacin

- Case reports
  - 46 yom 4 weeks Niacin 3 gram day
    - Elevated LFT's
    - Rechallenge- fulminant hepatic failure
    - Resolved with discontinuation
  - 2 cases of "masses"- focal fatty areas
    - Resolved with discontinuation
  - 2 cases of hepatitis after large doses of nicotinic acid
  - 8 cases of hepatitis on SR niacin
    - 3 cases re-challenged with IR and no recurrence

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Binding resins

- Cholestyramine (*Questran*)
- Colestipol (*Colestid*)
- Colesevelam (*Welchol*)
  - Bind bile acids in intestine- prevents 90% reabsorption
  - GI side effects

Binding resins

- Case reports
  - Colestipol
    - 65 yo male on drug x 3 months
    - LFT's 10 x normal
    - Resolved within 4 weeks of discontinuation
  - Colesevelam- *Welchol*
    - 1400 patients alone and with statin
    - Side effects same as placebo

Ezetimibe/*Zetia*

New agent

- Ezetimibe/*Zetia*
  - Selective cholesterol absorption inhibitor
    - Stops intestinal absorption, reduced cholesterol pool, increases hepatic LDL receptor activity
    - Not affect TG and fat-soluble vitamins
  - Clinical Efficacy
    - Monotherapy 15-20% decrease LDL
    - Combined with low-dose statin reduces LDL 20.7%
      - Vs. statin alone 6.7%
    - Combined with Simvastatin better than higher dose Atorvastatin at lowering LDL and increasing HDL

Ezetimibe/*Zetia*

- Zetia with Atorvastatin vs. increased Atorvastatin (Amer Heart J *n*=621) x 14 weeks
  - LFT elevations 1% vs. 0.3%
  - LDL decrease -23% vs. -8%

Ezetimibe & Simvastatin/*Vytorin*

Ezetimibe/*Zetia/Vytorin*

- Zetia with Simvastatin x 48 weeks (Madrid *n*=433) vs. simvastatin alone (after 14 weeks on a statin)
  - LFT elevations 0.3% vs. 0%
  - LDL decrease -24% vs. 3%
- Zetia with Simvastatin in CRD patients x 6 months (UK-HARP II *n*=203) vs. simvastatin alone
  - LFT elevations 0% vs. 4%
  - LDL decrease from baseline -40% vs. -26%

Ezetimibe/*Zetia/Vytorin*

- VYVA study- Ezetimibe and simvastatin vs. Atorvastatin
  - 8 arm parallel-group 10 week study (n=1902)
  - Pooled data:
    - ALT >3 x ULN
      - 0.1 (Atorvastatin) vs. 1.2 (Vytorin)
    - Reached LDL goal
      - 81.1% (Atorvastatin) vs. 89.7% (Vytorin)

Ballantyne, Abate. Dose-comparison study of the combinatin of ezetimibe and simvastatin vs atorvastain in patients with hypercholesterolemia: VYVA. AM Heart J (2005) 149;464-473.

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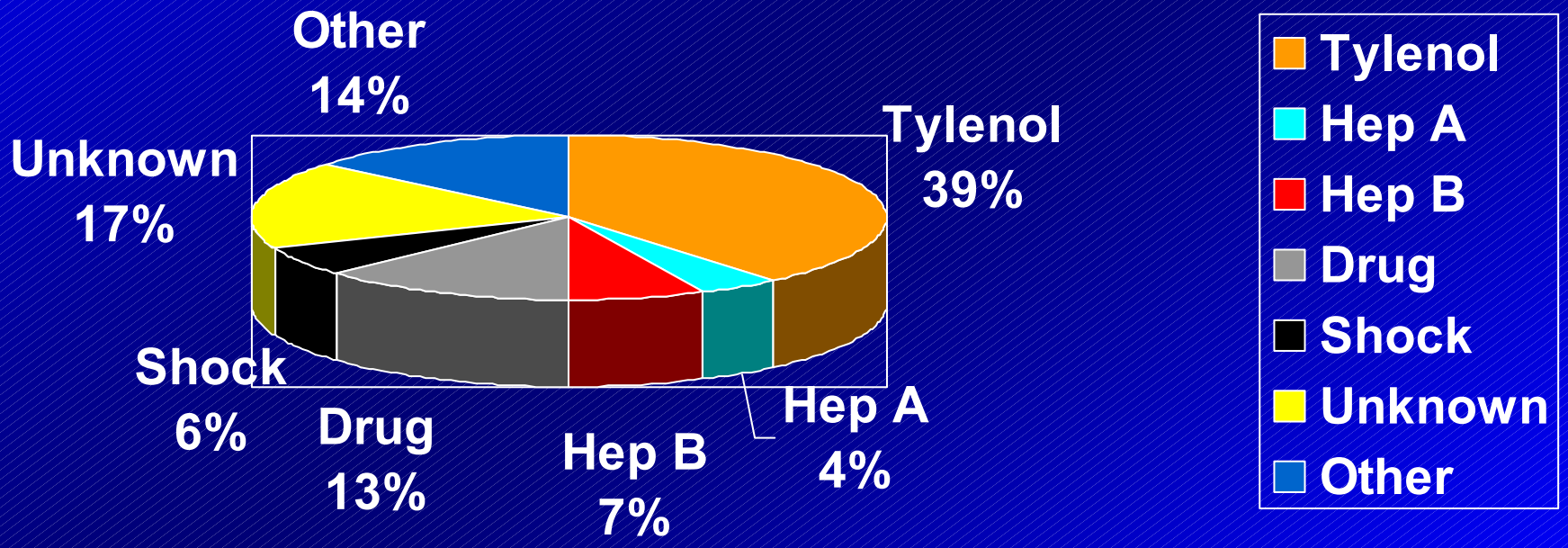
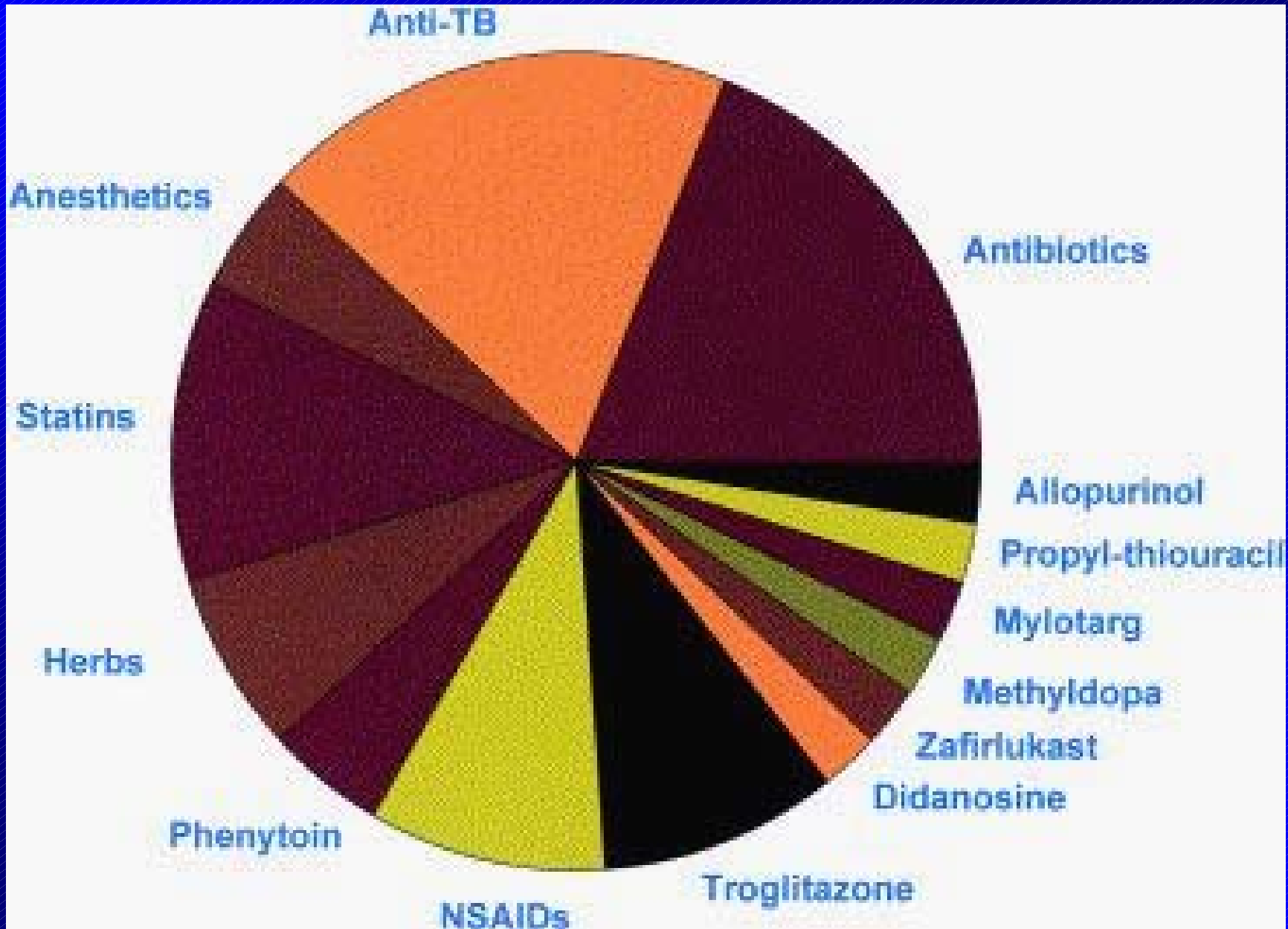
Big Picture

- Hepatotoxic reactions 1/130,000 general population
  - 1/114,000 for Statin drugs
  - 2-50/100,000 for NSAIDs
- Liver transplant
  - **1/206,000,000** per treatment with statin
    - Only 1 patient between 1990-2002 received a liver transplant due to “statin-hepatotoxicity” (of 51,741)
  - **6/372,000,000** per treatment with NSAID
- Most statins cause temporary increase LFT’s
  - Only long-acting Niacin unquestionably hepatotoxic

Acute Liver Failure in USA 1998-2001



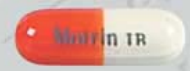
Cause of 44 idiosyncratic drug reactions resulting in acute liver failure 1998-2001



Drug Reactions

- Isoniazid
  - 20% increased LFT's
  - liver injury 1/100
  - fatality 1/10,000
- Survival
  - Better- (>50%)
    - Acetaminophen, Acute Hepatitis A, ischemia, pregnancy related
  - Worse- (<25%)
    - Idiosyncratic drug hepatotoxicity

McNeil Consumer



Gelcaps available in tamper evident packaging of 24, 50, and 100. Caplets available in tamper evident packaging of 24, 50, 100, 165, 250 and 300. Tablets available in tamper evident packaging of 24, 50, 100 and 165.

Motrin® IB

RX ROCHE

250 mg

375 mg

500 mg

Also available as 125 mg/5 mL suspension.

Naprosyn®
(naproxen)

Bayer Healthcare LLC

Tablets and Caplets available in 24, 50, 100, 150 and 200 count.

Caplets also available in 200 count.

Gelcaps available in 20, 40 and 80 count.

Easy-open Arthritis cap available.

Aleve®

NSAIDs

- Bromfenac- 1999 NSAID withdrawn for causing FHF
- NSAIDs in patients with known liver disease
    - Hepatorenal syndrome, diuretic resistant ascites, GI bleeding- variceal bleeding
- COX-2 inhibitors
    - Large trials no difference LFTs from placebo
    - 5 case reports of hepatocellular injury
        - All recovered with drug discontinuation

NSAIDs

- **Ibuprofen**
  - Acute hepatitis, cholestasis, vanishing bile duct syndrome, subfulminant hepatitis
    - Worsen LFT's in chronic hepatitis C patients
- **Sulindac** (*Clinoril*)
  - 91 cases to FDA
    - 43% cholestatic, 25% hepatocellular
    - 66% with hypersensitive features
    - 4 deaths- 1 FHF, 3 hypersensitivity
- **Diclofenac** (*Voltaren*)
  - 200 cases to FDA
    - 1-5/100,000
    - Fever, rash 25%
    - FHF after rechallenge
    - CYP 2C9

Other anti-inflammatory

- **Leflunomide** (*Arava*)
  - Rheumatoid arthritis
  - Trials 6.6% 2 x ULN, 4.4% 3 x ULN
  - European data 296 cases
    - 15 liver failure
    - 9 deaths liver-related
    - Most within 6 months initiation
    - 58% taking NSAIDs/MTX/ETOH, Hep C
  - Manufacturing recommendations
    - Monitor monthly x6, then QOM
      - » Dose reduce
      - » Use cholestyramine

Other anti-inflammatory

- Infliximab (*Remicade*)
  - No hepatotoxicity pre-marketing
  - Case reports
    - 2 patients- elevated LFT's (TB=19)
    - Resolution with discontinuation
- Zafirlukast (*Accolate*)
  - Leukotreine receptor antagonist for asthma
    - LFT elevation 3.3% during trials
    - Case reports = 6
      - 2 liver failure to transplant
      - Eosinophilia, massive necrosis, respond to CCS

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Statins in patients with baseline elevated LFT's

- Gastroenterology May 2004- Indiana-retrospective
  - 3 cohorts
    - Cohort 1- Elevated LFT's (40/35) on statin (342)
    - Cohort 2- Normal LFT's on statin (1437)
    - Cohort 3- Elevated LFT's without a statin (2245)
  - All followed for first 6 months of therapy
  - Mild elevation of LFT's (up to 10 x normal/baseline)
  - Severe elevation >10 x normal/baseline or TBili >3
    - Cohort 1- 4.7% mild, 0.6% severe
    - Cohort 2- 1.9% mild, 0.2% severe
    - Cohort 3- 6.4% mild, 0.4% severe (No statin therapy!)
  - Conclusion: Patients with baseline elevations of LFT's do not have worsened LFT's on statin therapy compared to those not on statin therapy

Statins in patients with baseline elevated LFT's

- Am J Med Sci- Indiana- Lovastatin
  - 3 Cohorts
    - Cohort 1- Elevated LFT's on Lovastatin (135)
    - Cohort 2- Baseline normal LFT's on Lovastatin (620)
    - Cohort 3- Elevated LFT's without Lovastatin (2644)
  - **12 month** follow up
  - Significant elevation of transaminases >5 x ULN/baseline or TBili >3
    - Cohort 1- mild 6.6%, severe 0% (baseline ALT 46)
    - Cohort 2- mild 3.0%, severe 0.3% (baseline ALT 18)
    - Cohort 3- mild 11%, severe 5.5% (baseline ALT 56)
  - Conclusion: Patients with baseline elevations of LFT's **IMPROVE** LFT's on statin therapy compared to those not on statin therapy

Statin Transaminitis in a large HMO

- American J of Medicine 2005, Kaiser Permanente of Colorado
  - 1997-2001 all patients on statin
  - Transaminases >10 x ULN
  - Evaluate for cause, dechallenge and rechallenge
  - N = 30,000 on a statin

Transaminitis, cont.

- 23,000 remained health plan member, not on chemotherapy and had LFT's checked (76%)
  - 2% ALT 3-10x ULN
  - 0.3% n= 62 ALT >10 ULN
    - 74% n= 46 not statin related
      - » 11 not on statin any more
      - » 15 cholelithiasis
      - » 8 viral hepatitis
    - 17 cases left
      - » 4 on cyclosporine, 1 on erythromycin, 1 diltiazem, 1 on indinavir, 1 on fluoxetine, 1 on cimetidine, 1 on verapamil
      - » Other 8: 2 in heart failure, ALL resolved within 8 weeks
      - » 13 were rechallenged- 3 with recurrence- 2 of these had second rechallenge with no recurrence on different statin

NASH and statins

- *Can J Gastroenterol* 2003
  - Atorvastatin vs. urso in NASH patients
  - Followed x 6 months
  - More patients in Atorvastatin group normalized LFTs

CAD patients

- Mortality study- *The American J of Cardiology* 1/2003
  - 15,000 1990-1996
  - Israel National Population Registry
  - 1,839 deaths
    - 57.4% cardiac
    - 34% noncardiac
      - 16% cancer
      - 5% CVA
      - 4% Sepsis
      - 0.6% PE
      - 6.5% other **(liver 0.03% 7)**
    - 8.6% unknown

CAD

- “Poly-portfolio” for secondary prevention
  - Am J Cardiology 2005
  - High dose statin, antihypertensive therapy, ASA, omega-3 fish oil, cardiac rehab, and diet
    - CHD decrease 84%
    - MI decrease 91%
    - Stroke decrease 77%
    - Pharmacologic therapy results in 93% decrease in second cardiac event, while lifestyle changes add 4% over 5 years

CAD

- UK population-based study
  - 1.18 million patients
  - 13,029 with MI 1996-2003
  - Statin use resulted in 39% lower all cause mortality
  - Longer duration = more benefit (19% per year after 2 years)
  - Same for atorvastatin vs. simvastatin

Hippisley-Cox. Effect of statins on the mortality of patients with ischaemic heart diesease: population based cohort study with nested case-controlanalysis. Heart 2006;92(6):752-8.

Current Statin use

- >10 million patients on statin therapy in the US alone
  - LFT's $60 each
  - Abnormal results often result in 10 x the cost to evaluate
  - Never proven cost-effective to "screen" for Acute Liver Failure
  - Acute Liver Failure occurs over days, not months

Future Statin Use

- Search for non-cholesterol benefits over last 2 months in medical literature:
  - Decreased sepsis mortality
  - Decreased fractures
  - Decreased Breast cancer
  - Decreased Colon Cancer
  - Decreased HTN
  - Improved Arthritis
  - Improved Ankylosing spondylitis
  - Treatment for acute subarachnoid hemorrhage
  - Treatment for polycystic ovarian syndrome
  - Treatment for migraines
  - Use in orthodontics
  - Treatment for lymphoma induced ascites
  - Lower risk of GI bleed

Future Statin Use

- Pravastatin/*Pravachol*
- Simvastain/*Zocor*
- Both to go generic this summer!

Evidence Based Conclusions

- Statin therapy does cause elevation of LFT's at high doses
- Statin therapy does not, in and of itself, result in liver failure, cirrhosis or chronic liver disease
- Monitoring of LFTs does not prevent liver damage, but may reveal underlying cause of liver disease
- Patients with baseline LFT elevation can be safely placed on statins

Clinical Conclusion

- Use Statins in patients who need them
  - Advise ETOH cessation
  - Stop statin temporarily if using CYP3A4 inhibitor
    - Clarithromycin, erythromycin, itraconazole, ect.
  - Switch statin if long-term CYP3A4 inhibitor drug necessary
    - Amiodarone, diltiazem, verapamil, fluoxetine, ect.
    - Switch to Pravachol, Lescol, Crestor
- Follow LFT's only at 6 weeks after initiation and dose changes or if symptomatic
- If elevated >3 x ULN **(AST- 120, ALT- 90)**
  - Work-up for chronic liver disease
  - Consider dose reduction of statins
  - Consider switching to Crestor

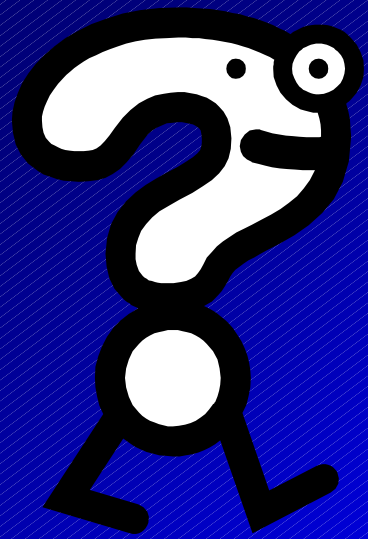
Workup of Chronic Liver Disease

- Check for Chronic hepatitis
  - Hep C antibody, Hep B surface Antigen
- Check for iron overload or Hemochromatosis
  - Ferritin, TIBC
- Check for underlying Autoimmune liver disease
  - ANA, anti-liver kidney antibody, AMA, SPEP
- Consider A1-antitrypsin deficiency, Wilson's disease, other drug (methotrexate, amiodarone, diltiazem)
- Consider referral to Hepatology to confirm NASH with biopsy

	P450 metabolism	Hepatotoxic
Lovastatin	**CYP3A4**	With inhibitor
Simvastatin	**CYP3A4**	With inhibitor
Pravastatin	Minimal/None	
Fluvastatin	CYP2C9	
Atorvastatin	**CYP3A4**	With inhibitor
Rosuvastatin	Minimal CYP2C9	
Ezetimibe	None	
Fenofibrate	None	
Gemfibrozil	Renal clear	
Colestipol	Non-absorbed	
Niacin	None	Yes

CYP3A4 inhibitors

- Amiodarone
- Cimetidine
- Ciprofloxacin
- Clarithromycin
- Cyclosporine
- Danazol
- Delavirdine
- Diltiazem
- Efavirenz
- Erythromycin
- Fluconazole
- Fluoxetine
- Fluovaxamine
- Grapefruit juice
- Indinavir
- Isoniazid
- Itraconazole
- Ketaconazole
- Metronidazole
- Micronazole
- Nefazodone
- Nelfinavir
- Nifedipine
- Norfloxacin
- Quinine
- Ritonavir
- Roxithromycin
- Saquinavir
- Sertralin
- Troleandomycin
- Verapamil
- Voriconazole
- Zafirlukast
- Zileuton



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