Update in Dyslipidemia

Update in Dyslipidemia

รัศมี โชวี่ห์ รุกลิ้งกิจ
จุฬาลงกรณ์มหาวิทยาลัย
Outline

• Approach to dyslipidemia
  • NCEP ATP III (2001 & 2004)
  • ESC/EAS dyslipidemia guideline (2011)
• Update on treatment and clinical trials
  • Statin and CKD
  • Statin and myopathy
• Update on triglycerides (2011)
Approaches to Dyslipidemia

- Complete Fasting Lipoprotein Analysis
- Rule Out Secondary Causes
- Assess Other CHD Risk Factors
- Therapeutic Lifestyle Changes
- Drug Therapy
- Monitoring
Lipoprotein Analysis

- Total cholesterol, Triglyceride, and HDL cholesterol
- Friedewald’s formula:
  \[ \text{LDL cholesterol} = \text{TC} - \text{HDL-C} - \frac{\text{TG}}{5} \]
- Obtained in all adults over age of 20 every 5 years
Who should be tested?

1. Patients with atherosclerotic vascular disease
2. High-risk patients
3. Patients with abnormal physical findings
Who should be tested?

1. Patients with atherosclerotic vascular disease
   1. Coronary artery disease
   2. Cerebrovascular disease
   3. Peripheral vascular disease
Who should be tested?

2. High-risk patients
   1. Age $\geq 45$ (males), $\geq 55$ (females)
   2. Family history of premature coronary artery disease: $< 55$ in males, $< 65$ in females
   3. Diabetes mellitus
   4. Hypertension
   5. Smoking
   6. Obesity
   7. Nephrotic syndrome or chronic renal failure
Who should be tested?

3. Patients with abnormal physical findings
   1. Corneal arcus
   2. Xanthelasma
   3. Xanthoma
Question

What is your diagnosis?

a) Tendon xanthoma
b) Tuberous xanthoma
c) Eruptive xanthoma
d) Palmar xanthoma
e) Xanthelasma
f) None of the above
Question
What is your diagnosis?

a) Tendon xanthoma
b) Tuberous xanthoma
c) Eruptive xanthoma
d) Palmar xanthoma
e) Xanthelasma
f) None of the above
Tendinous xanthoma
Tendinous xanthoma
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c) Eruptive xanthoma
d) Palmar xanthoma
e) Xanthelasma
f) None of the above
Eruptive xanthoma
Eruptive xanthoma

- Small yellowish round papules
- Found on the abdomen, back, buttocks, and pressure areas
- Due to accumulation of triglyceride in macrophages
- Pathognomonic for severe hypertriglyceridemia
What would you expect to see from a fundoscopic examination?

• A) Lipemia retinalis
• B) Cotton wool spots
• C) Proliferative retinopathy
• D) Subhyaloid hemorrhage
• E) Papilledema
What would you expect to see from a fundoscopic examination?

- A) Lipemia retinalis
- B) Cotton wool spots
- C) Proliferative retinopathy
- D) Subhyaloid hemorrhage
- E) Papilledema
Which one is lipemia retinalis?
Which one is lipemia retinalis?
Lipemia retinalis
What would you look for in this patient?

- A) Heavy alcohol use
- B) Undiagnosed diabetes
- C) Hypothyroidism
- D) Estrogen use
- E) Steroid use
What would you look for in this patient?

- A) Heavy alcohol use
- B) Undiagnosed diabetes
- C) Hypothyroidism
- D) Estrogen use
- E) Steroid use
Which of the following medications is/are associated with hypertriglyceridemia?

- A) Asparaginase
- B) Beta blocker
- C) Tamoxifin
- D) Sirolimus
- E) Bile acid-binding resin
Which of the following medications is/are associated with hypertriglyceridemia?

- A) Asparaginase
- B) Beta blocker
- C) Tamoxifen
- D) Sirolimus
- E) Bile acid-binding resin
Which of the followings would you recommend for this patient?

- A) Very low fat diet
- B) Good glycemic control
- C) Weight reduction
- D) Defer pregnancy
- E) Fibrate
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- A) Very low fat diet
- B) Good glycemic control
- C) Weight reduction
- D) Defer pregnancy
- E) Fibrate
Approaches to Dyslipidemia

• Complete Fasting Lipoprotein Analysis
• Rule Out Secondary Causes
• Assess CHD Risk Factors and Goals
• Therapeutic Lifestyle Changes
• Drug Therapy
• Monitoring
Secondary Causes of Dyslipidemia

- Diabetes mellitus
- Hypothyroidism
- Obstructive liver disease/cholestasis
- Chronic renal failure/nephrotic syndrome
- Lipodystrophies
- Drugs

ใช้ clinical ร่วมกับ lab บางตัว
Secondary Causes of Dyslipidemia

• Drugs:
  – Steroids
  – Ethanol
  – Estrogen, progestins
  – Testosterone
  – Thiazides
  – Retinoids
  – HIV protease inhibitors
Approaches to Dyslipidemia

- Complete Fasting Lipoprotein Analysis
- Rule Out Secondary Causes
- Assess CHD Risk Factors and Goals
- Therapeutic Lifestyle Changes
- Drug Therapy
- Monitoring
High Blood Cholesterol

Detection

Evaluation

Treatment


Final Report
Updated NCEP ATP III 2004

NCEP Report

Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines

Scott M. Grundy; James I. Cleeman; C. Noel Bairey Merz; H. Bryan Brewer, Jr; Luther T. Clark; Donald B. Hunninghake*; Richard C. Pasternak; Sidney C. Smith, Jr; Neil J. Stone; for the Coordinating Committee of the National Cholesterol Education Program

Endorsed by the National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, and American Heart Association
### Three Categories of Risk that Modify LDL-Cholesterol Goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD and CHD risk equivalents</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Multiple (2+) risk factors</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>Zero to one risk factor</td>
<td>&lt; 160</td>
</tr>
</tbody>
</table>
Question

Which of the following conditions is (are) considered coronary heart disease (CHD) equivalent?

a) Type 2 diabetes
b) Ischemic stroke from carotid artery disease
c) Abdominal aortic aneurysm
d) Peripheral artery disease
e) All of the above
Question
Which of the following conditions is (are) considered coronary heart disease (CHD) equivalent?

a) Type 2 diabetes
b) Ischemic stroke from carotid artery disease
c) Abdominal aortic aneurysm
d) Peripheral artery disease
e) All of the above
CHD Risk Equivalents

- Other clinical forms of atherosclerotic disease
  - peripheral arterial disease
  - abdominal aortic aneurysm
  - symptomatic carotid artery disease
- Diabetes
- (Multiple risk factors that confer a 10-year risk for CHD > 20%)
Major Risk Factors

• Cigarette smoking
• Hypertension (BP $\geq 140/90$ mmHg or on antihypertensive medication)
• Low HDL cholesterol (< 40 mg/dL)$^\dagger$
• Family history of premature CHD
  – CHD in male first degree relative < 55 yrs
  – CHD in female first degree relative < 65 yrs
• Age (men $\geq 45$ yrs; women $\geq 55$ yrs)

$^\dagger$ HDL cholesterol $\geq 60$ mg/dL counts as a “negative” risk factor; its presence removes one risk factor from the total count.
## LDL Cholesterol Goals and Cutpoints in Different Risk Categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
<th>LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC) (mg/dL)</th>
<th>LDL Level at Which to Consider Drug Therapy (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD Risk Equivalents</td>
<td>&lt; 100</td>
<td>≥ 100</td>
<td>≥ 130 (100–129: drug optional)</td>
</tr>
<tr>
<td>2+ Risk Factors</td>
<td>&lt; 130</td>
<td>≥ 130</td>
<td>≥ 160</td>
</tr>
<tr>
<td>0–1 Risk Factor</td>
<td>&lt; 160</td>
<td>≥ 160</td>
<td>≥ 190</td>
</tr>
</tbody>
</table>
Question

What is the target LDL-cholesterol goal in diabetic patients with CHD and metabolic syndrome?

a) <190 mg/dL
b) <160 mg/dL
c) <130 mg/dL
d) <100 mg/dL
e) <70 mg/dL
Question
What is the target LDL-cholesterol goal in diabetic patients with CHD and metabolic syndrome?

a) < 190 mg/dL
b) < 160 mg/dL
c) < 130 mg/dL
d) < 100 mg/dL
e) < 70 mg/dL
Candidates for Very Low LDL-C Goal of <70 mg/dL

- Very high risk patients
- Established atherosclerotic CVD
  - + multiple risk factors (esp. diabetes)
  - + severe and poorly controlled risk factors (e.g., cigarette smoking)
  - + metabolic syndrome (high TG, low HDL-C)
  - + acute coronary syndromes (PROVE IT)
NCEP ATP III: LDL-C Goals (2004 proposed modifications)

- **High Risk**
  - CHD or CHD risk equivalents (10-yr risk >20%)
- **Moderately High Risk**
  - ≥ 2 risk factors (10-yr risk 10-20%)
- **Moderate Risk**
  - ≥ 2 risk factors (10-yr risk <10%)
- **Lower Risk**
  - < 2 risk factors

Goal 160 mg/dL

Elevated Triglycerides

- Primary target of therapy: LDL cholesterol
- Secondary target: Non HDL cholesterol
- Achieve LDL goal before treating non-HDL cholesterol
Non HDL cholesterol

- Non-HDL cholesterol = VLDL + LDL cholesterol
  = (Total Cholesterol – HDL cholesterol)
- VLDL cholesterol: denotes atherogenic remnant lipoproteins
- Non-HDL cholesterol: secondary target of therapy when serum triglycerides are ≥ 200 mg/dL (esp. 200–499 mg/dL)
- Non-HDL cholesterol goal: LDL-cholesterol goal + 30 mg/dL
Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Three Risk Categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal (mg/dL)</th>
<th>Non-HDL-C Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD and CHD Risk Equivalent</td>
<td>&lt; 100</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>Multiple (2+) Risk Factors</td>
<td>&lt; 130</td>
<td>&lt; 160</td>
</tr>
<tr>
<td>0–1 Risk Factor</td>
<td>&lt; 160</td>
<td>&lt; 190</td>
</tr>
</tbody>
</table>
ESC/EAS Guidelines for the management of dyslipidaemias

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

Developed with the special contribution of: European Association for Cardiovascular Prevention & Rehabilitation†
ESC/EAS guideline

- Total cardiovascular risk
- Evaluation and treatment targets
Total CV risk levels

1. Very high risk
2. High risk
3. Moderate risk
4. Low risk
Total CV risk levels

1. Very high risk
   1. Documented CVD
   2. DM with target organ damage
   3. CKD (GFR <60 mL/min/1.73 m²)
   4. 10 year risk score ≥10%
Total CV risk levels

2. High risk
   1. Markedly elevated single risk factors (i.e. familial dyslipidemia or severe hypertension)
   2. 10 year risk score 5-10%
Total CV risk levels

3. Moderate risk
   1. 10 year risk score 1-5%

4. Low risk
   1. 10 year risk score <1%
Systemic Coronary Risk Estimation (SCORE)

- Estimates the 10 year risk of a first fatal atherosclerotic event
- Uses 5 parameters (age, sex, cholesterol, SBP, and smoking status)
- Not to be used in people with very high or high risk levels
Indication for lipid profiling

- Established CVD
- Type 2 diabetes mellitus
- Hypertension
- Smoking
- Obesity
- CKD
- Chronic inflammatory disease (SLE, RA, HIV, etc.)
- Family history of premature CVD
- Family history of familial dyslipidemia
- Age >40 (men) or 50 (women)
# Treatment targets

<table>
<thead>
<tr>
<th>Risk</th>
<th>LDL-C (mg/dL)</th>
<th>Non HDL-C (mg/dL)</th>
<th>Apo B (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high</td>
<td>&lt;70</td>
<td>&lt;100</td>
<td>&lt;80</td>
</tr>
<tr>
<td>High</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt;115</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
## Special Populations

<table>
<thead>
<tr>
<th></th>
<th>LDL-C target (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without CVD</td>
</tr>
<tr>
<td>Heterozygous FH</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>&lt;100</td>
</tr>
<tr>
<td>CKD (stage 2-4)</td>
<td></td>
</tr>
</tbody>
</table>
Approaches to Dyslipidemia

- Complete Fasting Lipoprotein Analysis
- Rule Out Secondary Causes
- Assess Other CHD Risk Factors
- Therapeutic Lifestyle Changes
- Drug Therapy
- Monitoring
Current pharmacologic treatments

1. Statins
2. Fibrates
3. Niacin
4. Resin
5. Others: cholesterol absorption inhibitor
Question

Statin use is associated with an increased risk for which of the followings?

a) Diabetes mellitus
b) Gallstone
c) Lymphoma
d) Suicide
e) Hemorrhagic stroke
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e) Hemorrhagic stroke
Update in Treatment

- **Statins**
  - Inhibit HMG CoA reductase
  - 1 mmol/l (38.6 mg/dL) reduction in LDL-C leads to 22% reduction in CVD risk
  - Increase risk for DM
  - Benefit:risk ratio ~ 9:1
  - No increased risk for gallstone
Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials


Summary
Background Trials of statin therapy have had conflicting findings on the risk of development of diabetes mellitus in patients given statins. We aimed to establish by a meta-analysis of published and unpublished data whether any relation exists between statin use and development of diabetes.

Methods We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials from 1994 to 2009, for randomised controlled endpoint trials of statins. We included only trials with more than 1000 patients, with identical follow-up in both groups and duration of more than 1 year. We excluded trials of patients with organ transplants or who needed haemodialysis. We used the I² statistic to measure heterogeneity between trials and calculated risk estimates for incident diabetes with random-effect meta-analysis.

Findings We identified 13 statin trials with 91 140 participants, of whom 42 78 (2 226 assigned statins and 20 32 assigned control treatment) developed diabetes during a mean of 4 years. Statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1.02–1.17), with little heterogeneity (P=0.11%) between trials. Meta-regression showed that risk of development of diabetes with statins was highest in trials with older participants, but neither baseline body-mass index nor change in LDL-cholesterol concentrations accounted for residual variation in risk. Treatment of 255 (95% CI 150–852) patients with statins for 4 years resulted in one extra case of diabetes.

Interpretation Statin therapy is associated with a slightly increased risk of development of diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events. Clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular disease should not change.
Statin and CKD
Question

What is the major cause of death in patients with CKD?

a) Coronary heart disease
b) Cerebrovascular disease
c) Infection
d) Cancer
e) Uremia
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a) Coronary heart disease
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c) Infection
d) Cancer
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Causes of death

Coronary Heart Disease (41%)
  Acute MI (8.6%),
  Atherosclerotic HD (3.4%),
  Cardiomyopathy (3.8%),
  Cardiac arrhythmia (5.2%)
  Cardiac arrest (20.4%)

Cerebrovascular Disease (6%)

Other Heart Disease (2%)

Infection (15%)

Cancer (4%)

Other (26%)

Unknown (7%)

Lipid abnormalities in CKD

<table>
<thead>
<tr>
<th></th>
<th>CKD</th>
<th>Nephrotic syndrome</th>
<th>Hemo-dialysis</th>
<th>Peritoneal dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>↑↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Rosuva</td>
<td>Atorva</td>
<td>Simva</td>
<td>Lova</td>
</tr>
<tr>
<td>---------------------------</td>
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<td>--------</td>
<td>-------</td>
<td>------</td>
</tr>
<tr>
<td><strong>T 1/2, h</strong></td>
<td>20.8</td>
<td>15–30</td>
<td>2–3</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Urinary excretion, %</strong></td>
<td>10</td>
<td>&lt;2</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td><strong>CYP-3A4 metabolism</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>CYP metabolism</strong></td>
<td>2CY9</td>
<td>3A4</td>
<td>3A4</td>
<td>3A4</td>
</tr>
</tbody>
</table>

Harper and Jacobson. JACC 2008'51:2375
### Table 7: Dosing Modifications for Lipid-Lowering Drugs in CKD

<table>
<thead>
<tr>
<th>Agent</th>
<th>GFR 60–90 ml/min/1.73 m²</th>
<th>GFR 15–59 ml/min/1.73 m²</th>
<th>GFR &lt;15 ml/min/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>No</td>
<td>Not defined</td>
<td>Not defined</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>No</td>
<td>↓ to 50%</td>
<td>↓ to 50%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>No</td>
<td>5–10 mg</td>
<td>5–10 mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>No</td>
<td>No</td>
<td>5 mg</td>
</tr>
<tr>
<td><strong>Nonstatins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>No</td>
<td>No</td>
<td>↓ to 50%</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>↓ to 50%</td>
<td>↓ to 25%</td>
<td>Avoid</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Omega-3 FAs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Statin use in nondialysis CKD patients: a meta-analysis

- 26 studies, n = 25,017
- ↓ all-cause mortality
  - RR=0.81, 95%CI = 0.74-0.89
- ↓ CVD death
  - RR=0.80, 95%CI = 0.70-0.90
- Adverse events were not significantly different

Navaneethan et al. Cochrane Database Syst Rev 2009
Statin use in hemodialysis patients

- 2 clinical trials
  - 4D (n=1,225, atorvastatin 20 mg/d)
  - AURORA (n=2,776, rosvuastatin 10 mg/d)
- ↓ LDL-C 42-43%
- No significant decrease in CVD events
  - 4D RR=0.92 (95%CI 0.77-1.10, P=0.37)
  - AURORA RR=0.96 (95%CI 0.84-1.11, P=0.59)

SHARP

- Study of Heart and Renal Protection
- Simvastatin and ezetimibe vs placebo
- N=9270, 6247 no dialysis, 3023 dialysis
- eGFR 27 ml/min/1.73 m²
- F/U 4.9 yr
The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial


Summary
Risk ratio 0.83 (0.74 – 0.94)
Logrank 2P=0.0022
CKD and cardiovascular diseases

Statin and myopathy
Statin-associated myopathy

Classification by AHA/ACC/NHLBI

1. myalgia
2. myositis
3. rhabdomyolysis
Statin-associated myopathy

- Found in ~ 10%
- Muscle complaints in clinical practice are much more common than reported in clinical trials and postmarketing surveillance

Risk factors for statin-associated myopathy

1. elderly thin female
2. multiple medical problems
   - renal insufficiency
   - hepatic dysfunction
   - hypothyroidism
3. Polypharmacy
4. Genetic predisposition: $SLCO1B1$, etc.
<table>
<thead>
<tr>
<th>Statin</th>
<th>Licensed dose range (% LDL cholesterol reduction)*</th>
<th>Metabolism</th>
<th>Most important drug interactions increasing myopathy risk†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>20–80 mg daily (30% with 40 mg)</td>
<td>Mainly CYP3A4</td>
<td>Potent inhibitors of CYP3A4†</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10–80 mg daily (41% with 40 mg)</td>
<td>Mainly CYP3A4</td>
<td>Potent inhibitors of CYP3A4</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>20–80 mg daily (34% with 40 mg)</td>
<td>Sulphation, biliary, and urinary excretion</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>40–80 mg daily (23% with 40 mg)</td>
<td>CYP2C9 (some CYP2C8 and CYP3A4)</td>
<td>Inhibitors of CYP2C9</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10–80 mg daily (38% with 10 mg)</td>
<td>CYP3A4</td>
<td>Potent inhibitors of CYP3A4</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5–40 mg daily (45% with 10 mg)</td>
<td>Minimal metabolism (via CYP2CP and some CYP2C19) and biliary excretion</td>
<td></td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>2–4 mg daily (42% with 2 mg)</td>
<td>Minimal metabolism (via CYP2C8 and CYP2C9), lactonisation, and biliary excretion</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

Armitage. Lancet. 2007;370:1781
Drugs that increase risk of statin-associated myopathy

- Fibrates, esp. Gemfibrozil
- Niacin
- Macrolide antibiotics
- Azole antifungals
- Cyclosporine
- HIV protease inhibitors
- Amiodarone

- Verapamil
- Diltiazem
- Digoxin
- Warfarin
- Alcohol
- Grapefruit juice
Management of statin-associated myopathy

1. Check CK level
2. Rule out other common causes
2. Discontinue if CPK > 10x ULN
3. Follow symptoms and CPK levels
Other causes of CK elevation

1. Physical activity, trauma, falls, accidents
2. Seizure, shaking chills
3. Hypothyroidism
4. Infections
5. Carbon monoxide poisoning
6. Polymyositis, dermatomyositis
7. Alcohol abuse
8. Drug abuse (cocaine, amphetamine, heroin, PCP)

McKenney et al. Am J Cardiol. 2006;97:89C.
Other alternatives in statin-associated myopathy

1. Fluvastatin or pravastatin at low doses
2. Fluvastatin XL 80 mg/d
3. Low dose rosuvastatin (5 mg) or atorvastatin (10 mg) daily, every other day, or weekly
4. A combination of nonstatin drug plus the highest tolerated dose of statin
5. Nonstatin drugs

Non-statin alternatives in statin-associated myopathy

1. Ezetimibe
2. Bile acid-binding resin
3. Plant stanols
4. Red yeast rice
5. Coenzyme Q10
6. Vitamin D

Plant sterols/stanols

- Plant’s equivalent of cholesterol
- Found in vegetable oils, nuts, seeds, and leafy vegetables
- Main plant sterols are β-sitosterol, campesterol, and stigmasterol
- Sterols can be hydrogenated to stanols
- Lower cholesterol by decreasing cholesterol absorption
Plant sterols/stanols

- NCEP/ATP III recommends 2 g or more of plant sterols/stanols daily
- Fortified foods: tub margarine, spread, yogurt drinks, juice, chocolate, cheese, and granola bars
- Can lower LDL-C
Red yeast rice

• Red fermented rice

• Its color is due to cultivation with the mold *Monascus purpureus*

• Contains monacolins, which is identical to lovastatin from *Aspergillus*

• Traditional chinese medicine
Question

Red yeast rice is found in which of the followings?

a) ไวน์แดง
b) ซอสใสยี่นตายี่
c) เตาหูยิ้ม
d) ผงหมักหมูแดง
e) ถูกทุกข์ข้อ
Question

Red yeast rice is found in which of the followings?

a) ไวน์แดง
b) ซอสใสเย็นตาโฟ
c) เตาหูยี
d) ผงหมักหมูแดง
e) ถูกทุกข์ช้อ
Update in Treatment

• Fibrates
  • Primary target is peroxisome proliferator activated receptor (PPAR)-alpha
  • A meta-analysis shows a 10% reduction in major cardiovascular events
Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis


Summary

Several clinical trials have reported inconsistent findings for the effect of fibrates on cardiovascular risk. We undertook a systematic review and meta-analysis to investigate the effects of fibrates on major clinical outcomes.

Methods

We systematically searched Medline, Embase, and the Cochrane Library for trials published between 1950 and March, 2010. We included prospective randomised controlled trials assessing the effects of fibrates on cardiovascular outcomes compared with placebo. Summary estimates of relative risk (RR) reductions were calculated with a random effects model. Outcomes analysed were major cardiovascular events, coronary events, stroke, heart failure, coronary revascularisation, all-cause mortality, cardiovascular death, non-vascular death, sudden death, new onset albuminuria, and drug-related adverse events.

Findings

We identified 18 trials providing data for 45038 participants, including 2870 major cardiovascular events, 4552 coronary events, and 3880 deaths. Fibrate therapy produced a 10% RR reduction (95% CI 0–18) for major cardiovascular events (p=0.048) and a 13% RR reduction (7–19) for coronary events (p<0.0001), but had no benefit on stroke (−3%, −16 to 9; p=0.69). We noted no effect of fibrate therapy on the risk of all-cause mortality (0%, −8 to 7; p=0.92), cardiovascular mortality (3%, −7 to 12; p=0.59), sudden death (11%, −6 to 26; p=0.19), or non-vascular mortality (−10%, −21 to 0.5; p=0.063). Fibrates reduced the risk of albuminuria progression by 14% (2–25; p=0.028). Serious drug-related adverse events were not significantly increased by fibrates (1743 participants; 223 events; RR 1.21, 0.91–1.61; p=0.19), although increases in serum creatinine concentrations were common (1.99, 1.46–2.70; p<0.0001).

Interpretation

Fibrates can reduce the risk of major cardiovascular events predominantly by prevention of coronary events, and might have a role in individuals at high risk of cardiovascular events and in those with combined dyslipidaemia.
Update in Treatment

- Statin and fibrate (ACCORD-Lipid)
  - Did not reduce cardiovascular events
  - Possible benefit in men and those with high TG (>200 mg/dL) and low HDL-C (<35 mg/dL) at baseline
Update in Treatment

- Niacin
  - Receptor is GPR109A
  - Lowers cholesterol, and triglyceride, increases HDL-C
  - Whether adding niacin to standard treatment resulting in clinical benefit remains unproven
Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy

The AIM-HIGH Investigators

ABSTRACT

BACKGROUND
In patients with established cardiovascular disease, residual cardiovascular risk persists despite the achievement of target low-density lipoprotein (LDL) cholesterol levels with statin therapy. It is unclear whether extended-release niacin added to simvastatin to raise low levels of high-density lipoprotein (HDL) cholesterol is superior to simvastatin alone in reducing such residual risk.
Update in Treatment

- Cholesterol absorption inhibitor
  - Only medication available is ezetimibe
  - Receptor is NPC1L1
  - Lowers total and LDL cholesterol
Outline

- Approach to dyslipidemia
  - ESC/EAS dyslipidemia guideline (2011)
- Update on treatment and clinical trials
  - Statin and CKD
  - Statin and myopathy
- Update on triglycerides (2011)
Triglycerides

AHA Scientific Statement

Triglycerides and Cardiovascular Disease
A Scientific Statement From the American Heart Association

Michael Miller, MD, FAHA, Chair; Neil I. Stone, MD, FAHA, Vice Chair; Christie Ballantyne, MD, FAHA; Vera Bittner, MD, FAHA; Michael H. Criqui, MD, MPH, FAHA; Henry N. Ginsberg, MD, FAHA; Anne Carol Goldberg, MD, FAHA; William James Howard, MD; Marc S. Jacobson, MD, FAHA; Penny M. Kris-Etherton, PhD, RD, FAHA; Terry A. Lennie, PhD, RN, FAHA; Moshe Levi, MD, FAHA; Theodore Mazzone, MD, FAHA; Subramanian Pennathur, MD, FAHA; on behalf of the American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Nursing, and Council on the Kidney in Cardiovascular Disease

Circulation, 2011;123:2292-2333.
Triglyceride and CAD

- Whether triglyceride is an independent risk factor for CAD remains unclear (data are inconsistent)
- More data on nonfasting triglyceride
- Triglyceride-rich lipoproteins and remnant-lipoprotein particles are atherogenic
Causes of hypertriglyceridemia

- Genetic
- Acquired
- Both
Acquired causes of hypertriglyceridemia

- Hypothyroidism
- Pregnancy
- Poorly controlled diabetes mellitus
- Renal diseases
- Drugs
- Alcohol excess
- Metabolic syndrome
- Lipodystrophy (genetic and acquired)
- Others: SLE, chronic infections, etc.
## Drugs associated with hypertriglyceridemia

- Estrogens (oral)
- Raloxifene
- Tamoxifen
- Steroids
- Thiazides
- Bile acid resins
- Retinoic acid
- Protease inhibitors
- Interferon
- Beta blockers
- L-asparaginase
- Antipsychotics
- Sirolimus
Management of hypertriglyceridemia

- Weight loss
  - 1 kg weight loss ↓ TG 1.5 mg/dL
  - 5-10% weight loss ↓ TG 20-30%
- Exercise
  - Jogging 10 miles/week ↓ TG 20%
  - Most effective when baseline levels are elevated
- Diet
- Medications
Dietary management of hypertriglyceridemia

- **Avoid**
  - alcohol
  - added sugars
  - fructose (<100 g/d)
  - saturated fatty acids
  - trans fatty acids
Question

น้ำตาลชนิดใดที่เพิ่มระดับถูกกลีเซอริท์

a) glucose
b) fructose
c) galactose
d) sucrose
e) maltose
Question

น้ำตาลชนิดใดที่เพิ่มระดับทรกลีเซอริด

a) glucose
b) fructose
c) galactose
d) sucrose
e) maltose
All sugars are not created equal

- Monosaccharides
  - glucose
  - fructose: most common naturally occurring sugar
  - galactose

- Disaccharides
  - sucrose (glucose + fructose)
  - lactose (glucose + galactose)
  - maltose (glucose + glucose)

- fructose and sucrose, but not glucose, tend to exacerbate postprandial lipemia
Question

น้ำตาลฟรุตโตศาสพบใน

a) น้ำผึ้ง
b) น้ำตาลสด
c) น้ำอ้อย
d) น้ำผลไม้
e) น้ำตาลเทียม
Question

น้ำตาลฟรุตโตผสมใน

a) น้ำผึ้ง
b) น้ำตาลสด
c) น้ำอ้อย
d) น้ำผลไม้
e) น้ำตาลเทียม
Fructose

- Fruit sugar
- Monosaccharide
- Isomer of glucose (same formula but different structure)
- Component of sucrose or table sugar (glucose + fructose)
- Found in fruits, vegetables, and honey
Fructose vs. Glucose

- Glucose metabolism is regulated by phosphofructokinase and fructose is not
- Fructose enhances lipogenesis and triglyceride synthesis
High fructose corn syrup (HFCS)
- A family of mixtures of varying amounts of fructose and glucose
- HFCS 55 and HFCS 42
- Sweetener
- Somewhat cheaper than sucrose
- Corn → corn starch → corn syrup → HFCS
- Found in beverages, breads, cereals, breakfast bars, yogurt, etc.
High fructose corn syrup (HFCS)
Different sugars, different effects

10 weeks of glucose or fructose-sweetened beverages

Different sugars, different effects

10 weeks of glucose or fructose-sweetened beverages

Glucose vs. Fructose

- **Glucose** $\uparrow$ glucose and insulin levels
- **Fructose** $\uparrow$ triglyceride and LDL-C levels
- No metabolic differences between sucrose and high fructose corn syrup
Trans fatty acids

Trans fatty acids

- No intrinsic health value
- Should be <0.5-1% of total energy intake per day
- <500 mg per serving → labeled as 0

Trans fatty acids

- Increase triglyceride, LDL-C and lipoprotein(a)
- Lower HDL-C
- Reduce LDL particle size
- Promote inflammation
- Cause endothelial dysfunction
- Associated with CHD

What can I eat?
Dietary management of hypertriglyceridemia

- **Increase**
  - fiber
  - omega-3 PUFA
  - Mediterranean style diet (rich in MUFA, PUFA and fiber: fruits, vegetables, nuts, whole grains, and olive oil)
Fiber

- Reduce postprandial hypertriglyceridemia
- Lower cholesterol by increasing bile acid output
- 3-9% reduction in LDL-C
Omega-3 PUFA

- Marine-derived
  - EPA (eicosapentaenoic acid)
  - DHA (docosahexaenoic acid)
- Nonmarine-derived
  - α-linolenic acid (plant-based)

- 1 g of EPA/DHA reduce TG by 5-10%
- 2-4 g EPA/DHA
Question

Omega-3 fatty acids are found in which of the followings?

a) ปลาทะเลน้ำลึก
b) ปลาทะเลทั่วๆไป
c) ปลาทะเลในอ่าวไทย
d) ปลาทะเลที่นครศรีธรรมราชเท่านั้น
e) ปลาทะเลและปลา념จืด
Omega-3 fatty acids are found in which of the followings?

a) ปลาทะเลน้ำลึก
b) ปลาทะเลทั่วๆไป
c) ปลาทะเลในอ่าวไทย
d) ปลาทะเลที่นครศรีธรรมราชท่านั้น
e) ปลาทะเลและปลาเนื้อจืด
Omega-3 PUFA

- Fish that have high omega-3 fatty acids
- Fish such as salmon, mackerel, tuna, and sardines.
Dietary management of hypertriglyceridemia

- **Avoid**
  - alcohol
  - added sugars
  - saturated fat
  - trans fatty acids
  - fructose

- **Increase**
  - fiber
  - omega-3 PUFA
  - Mediterranean style diet
Management of severe hypertriglyceridemia

• Diet control: medium-chain triglyceride
• Fibrate
• Niacin
• Omega-3 fatty acids
Medium-chain triglycerides

- 6-12 carbon fatty acid esters of glycerol
- Can diffuse to the portal system without absorbed into the lymphatic system
- Found in coconut oil and palm kernel oil
- Caproic acid (C6), Caprylic acid (C8), Capric acid (C10), and Lauric acid (C12)
Medium-chain triglycerides
Thank you for your attention
Wanted!

086-811-8875 or wkhovid@gmail.com
Wanted!

086-811-8875 or wkhovid@gmail.com
Dietary Fiber

- Indigestible portion of plant food
  - Soluble (viscous)
  - Insoluble

- Soluble fiber is fermented in the colon into gases
- Insoluble fiber is not fermented, is metabolically inert, and increases bulk
- Polysaccharides (cellulose, pectins) and lignins
Soluble Fiber

เตียนแกลล์คหอย
Soluble Fiber

- Legumes (peas, beans)
- Oats, rye, barley
- Fruit and fruit juices (plums, berries, apples, pears, bananas, persimmon, prune juice)
- Vegetables (broccoli, carrots, artichokes)
- Root vegetables (konjac, sweet potatoes, onions)
- Psyllium seed husk, flax seed coat
Insoluble Fiber
Insoluble Fiber

- Whole grain foods
- Wheat and corn bran
- Nuts and seeds
- Flaxseed
- Vegetables (green beans, cauliflower, zucchini, celery)
- Fruits (Avocado, banana)
Dietary fiber and lipid processing

- Some soluble fiber can form viscous solutions and reduce the rate of lipid emulsification with a resulting lowering of fat lipolysis.

- Certain proteins present in dietary fiber can inhibit pancreatic lipase activity.

- Dietary fiber can bind bile acids and disrupt the micellization process and intestinal uptake of lipids.
Macronutrient management of hypertriglyceridemia

- Several studies of high carbohydrate diets have shown increased TG levels, but recent studies (DASH, OmniHeart and WHI) didn’t
- High fiber intake (30 g/d)
- High protein intake (plant based, >15%)
- High in fruits, vegetables, and grains
- Moderate intake of unsaturated fat (30-35%)
Low CHO vs low fat

- Low CHO diets produce a more robust triglyceride lowering effect than low fat diets.
- Diets that produce significant and sustained weight loss offer the most favorable reductions in triglyceride levels.