DEFINITION

- Dyslipidemia is defined as
  - elevated TC, LDL-C, or TG
  - OR decreased HDL-C
  - OR combination of these abnormalities.
• Dyslipidemia ➔ atherosclerosis ➔
  • coronary disease,
  • cerebrovascular disease
  • peripheral vascular disease.

• Every 1% ↑ in blood cholesterol ➔ 1-2% ↑ in incidence of CHD.
• Every 1% ↓ in HDL-C ➔ 1-2% ↑ in incidence of CHD.

PATHOPHYSIOLOGY: LIPOPROTEINS

- Apo A for HDL
- Apo B100 for LDL & VLDL
LIPID METABOLISM

Lipoproteins are classified to:

<table>
<thead>
<tr>
<th></th>
<th>Composition</th>
<th>Density</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>TG &gt;&gt; C, CE</td>
<td>Low</td>
<td>Large</td>
</tr>
<tr>
<td>VLDL</td>
<td>TG &gt; CE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDL</td>
<td>CE &gt; TG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>CE &gt;&gt; TG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>CE &gt; TG</td>
<td>High</td>
<td>Small</td>
</tr>
</tbody>
</table>

Apo B lipoproteins (Non HDL)

Apo A lipoprotein

---

![Lipid Metabolism Diagram]

- Chylomicron
  - VLDL
  - IDL
  - LDL
  - HDL

Physiology of Lipoprotein Metabolism

- HMG-CoA
  - TG
  - Chol
  - LDL-R
  - Fibrate & Niacin
  - LPL
  - FA
  - HDL
  - LPL

Blood vessel

- Muscle and adipose tissue

Liver

Intestine

Statins

Bile duct

Hepatic portal vessels

Ezetimibe

Resins

HMG-CoA Reductase

TG, Chol, LPL, FA

Physiology of Lipoprotein Metabolism

Muscle and adipose tissue
THE STORY OF LIPIDS

- **Chylomicrons** transport fats from the intestinal mucosa to liver & adipose tissues
- **VLDL** is formed in the liver from TG & cholesterol then released into blood, hydrolyzed by LPL to become IDL then LDL (LDL then carries cholesterol to the body’s cells).
- **HDL** carry cholesterol back to the liver for excretion (Reversible cholesterol transport).

- When oxidized LDL-C gets high → atheroma formation in the artery walls → atherosclerosis.
- HDL-C remove cholesterol from the atheroma.
- Atherogenic cholesterol → LDL, VLDL, IDL

Types & causes of dyslipidemia

1ry dyslipidemia (Genetic, Familial)

2ry dyslipidemia

1- Diet
2- Disease
3- Drugs
1RY DYSLIPIDEMIA

Polygenic hypercholesterolemia & atherogenic dyslipidemia, are the most common & the result of interaction between genes & lifestyle.

1. Polycigenic hypercholesterolemia:
   - most prevalent form,
   - ↑ LDL-C (130-250 mg/dl)

2. Atherogenic dyslipidemia:
   - 25% of patients who have lipid disorder,
   - moderate ↑ TG & LDL-C with ↓ HDL-C

3. Familial hypercholesterolemia: marked ↑ LDL-C (250-450 mg/dl)

4. Familial Hypertriglyceridemia (chylomicronemia) (due to LPL deficiency): ↑ chyomicrons & VLDL

5. Familial combined hyperlipidemia: ↑ VLDL & LDL-C

6. Hypoalphalipoproteinemia: ↓ HDL-C

2ry dyslipidemia

Diseases

1- Endocrinal: DM & Hypothyroidism
2- Renal: Chronic RF & Nephrotic syndrome
3- Hepatocellular disease
4- SLE
5- Pregnancy

Drugs

1- Accutane (isotretenoin)
2- BB
3- Cortisone
4- Oral Contraceptives
5- Diuretics
DIETARY SOURCES OF ChOLESTEROL

<table>
<thead>
<tr>
<th>Type of Fat</th>
<th>Main Source</th>
<th>Effect on Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monounsaturated</td>
<td>Olives &amp; olive oil, peanuts &amp; peanut oil, canola oil, cashews, almonds, avocados</td>
<td>Lowers LDL, Raises HDL</td>
</tr>
<tr>
<td>Polyunsaturated</td>
<td>Corn oil, cottonseed oil, soybean, fish</td>
<td>Lowers LDL, Raises HDL</td>
</tr>
<tr>
<td>Saturated</td>
<td>Milk, chocolate, butter, ice cream, cheese, red meat, coconuts, coconut milk, coconut oil, egg yolks, chicken skin</td>
<td>Raises both LDL and HDL</td>
</tr>
<tr>
<td>Trans</td>
<td>Cookies, Donuts, Most margarines; partially hydrogenated vegetable oil; deep-fried chips; fast foods; most commercial baked goods</td>
<td>Raises LDL</td>
</tr>
</tbody>
</table>

CLINICAL PRESENTATION

- Most patients **asymptomatic**

- May presented with:
  - **xanthomata** or
  - Premature arcus senilis
  - **atherosclerotic** complications

- **Metabolic syndrome: ≥ 3 of the following**
  1. Atherogenic dyslipidemia
  2. Abdominal obesity
     - M: >102 cm (>40 in)
     - F: > 88 cm (>35 in)
  3. Hypertension
  4. DM

![Image of skin conditions]
DIAGNOSIS

- A fasting (8-12 h) lipoprotein profile (FLP) including TC, TG, LDL & HDL
  - (FLP should be measured in all adults 20 y of age or older at least once /5 years).
    - LDL: < 160
    - TC: 200 - 240
    - HDL: 40 - 60
    - TG: < 200

- Usually we can measure: TC, TG & HDL-C, then:
  - VLDL = TG ÷ 5;
  - LDL = TC – (VLDL + HDL).
  - Non-HDL-C = TC minus HDL-C

MANAGEMENT OF HYPERLIPIDEMIA

- The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III):
  - Used “Framingham”10-year risk score for assessment of CVD risk
  - Focused on LDL-C goal and target

- New 2013 ACC/AHA guidelines:
  - Used “Pooled Cohort Equations” to calculate the 10 year ASCVD risk
  - No specific LDL cholesterol target & Measure lipids during follow-ups to assess adherence to treatment, not to achieve a specific LDL target
  - Initiate either moderate-intensity or high-intensity statin therapy for patients who fall into the four categories
3- Treatment of hyperlipidemia

**Therapeutic lifestyle change (TLC)**

- Diet modification:
  - Replacing saturated with unsaturated fats
  - Restricts total fat intake to 25% - 35% of calories
  - Increase fresh vegetables & fruits
- Weight reduction:
- Smoking cessation
- Physical activity increase:

**Drug therapy**

- Statin
- Fibrates
- Resins
- Niacin
- Ezetimibe

### THERAPEUTIC LIFESTYLE CHANGE (TLC)

1. **Diet:**
   - Replacing saturated with unsaturated fats
   - Restricts total fat intake to 25% - 35% of calories
   - Increase fresh vegetables & fruits

2. **Smoking cessation**

3. **Weight reduction:**
   - Reduce body weight 10% within 6 ms
   - Normal weight is defined as
     - BMI: 18.5 - 24.9, and
     - Waist circumference <40 inches for male & <35 inches for female

4. **Increasing physical activity**
**Mechanism Of Action Of Antihyperlipidemic Drugs**

1) **Statins**  
HMG-CoA reductase inhibitors  
- Atorvastatin  - Pravastatin  
- Lovastatin  - Simvastatin  
- **Rosuvastatin**

**Examples**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>1) Statins</th>
<th>2) Fibrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ HMG-CoA reductase enz [rate limiting enz]</td>
<td>↓ cholesterol synthesis</td>
<td>↓ TG through:</td>
</tr>
<tr>
<td>↓ HMG-CoA reductase enz [rate limiting enz]</td>
<td>compansatory ↑ in LDL receptors on hepatocytes</td>
<td>1. ↑ LPL enz. ↓ LDL</td>
</tr>
<tr>
<td>↓ LDL &amp; cholesterol</td>
<td>↑ LDL &amp; cholesterol</td>
<td>2. ↓ Hepatic synthesis of T.G &amp; VLDL</td>
</tr>
<tr>
<td><strong>NB.: better take at night (as cholesterol synthesis is maximum at night) except atorvastatin &amp; rosuvastatin (long t ½)</strong></td>
<td></td>
<td>3 ↑ HDL</td>
</tr>
</tbody>
</table>

**Examples**

- Etofibrate  - Fenofibrate  
- Gemfibrozil  - Bezafibrate  
- Clofibrate (should not be used as it may cause cholangiocarcinoma and other GIT cancers)
<table>
<thead>
<tr>
<th><strong>1) Statins</strong></th>
<th><strong>2) Fibrates</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HMG-CoA reductase inhibitors</strong></td>
<td><strong>Side effects</strong></td>
</tr>
<tr>
<td>1. Hepatotoxic ➔ ↑ serum transaminases</td>
<td>1. Hepatotoxic ➔ ↑ serum transaminases</td>
</tr>
<tr>
<td>4. Cholesterol gallstones &amp; cholecystitis</td>
<td><strong>Side effects</strong></td>
</tr>
<tr>
<td>5. Displace other drugs from plasma proteins</td>
<td><strong>Side effects</strong></td>
</tr>
</tbody>
</table>

**FDA EXPANDS ADVICE ON STATIN RISKS, 2014**

- **Routine monitoring of liver enzymes is no longer needed.** Such monitoring has not been found to be effective in predicting or preventing the rare occurrences of serious liver injury associated with statin use.
- **Cognitive impairment** (as memory loss, forgetfulness & confusion) has been reported by some statin users.
- **Increased risk of raised blood sugar & the development of Type 2 diabetes** have been reported in some cases treated with statin.
**PHARMACOKINETIC DATA ON STATINS**

<table>
<thead>
<tr>
<th>Origin</th>
<th>Lovastatin (lovastatin®)</th>
<th>Simvastatin (zocor®)</th>
<th>Fluvastatin (lescol®)</th>
<th>Pravastatin (lipostat®)</th>
<th>Atorvastatin (lipitor®)</th>
<th>Rosuvastatin (crestor®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Prodrug</td>
<td>Prodrug</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
</tr>
<tr>
<td>Metabolite</td>
<td>Active</td>
<td>Active</td>
<td>Inactive</td>
<td>Inactive</td>
<td>Active</td>
<td>Active</td>
</tr>
<tr>
<td>Half life (hour)</td>
<td>3</td>
<td>2</td>
<td>1.2</td>
<td>1.8</td>
<td>7-14</td>
<td>14-20</td>
</tr>
<tr>
<td>Protein binding %</td>
<td>&gt;95%</td>
<td>&gt;95%</td>
<td>&gt;90%</td>
<td>50%</td>
<td>96%</td>
<td>88%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP 3A4</td>
<td>CYP 3A4</td>
<td>CYP 2C9</td>
<td>sulfation</td>
<td>CYP 3A4</td>
<td>CYP 2C9/2C19</td>
</tr>
</tbody>
</table>

**NB.:** better take at night (as cholesterol synthesis is maximum at night) except atorvastatin & rosuvastatin (long t½)

Grape fruit juice, HME inducers & inhibitors ????
FOUR STATIN BENEFIT GROUPS:

1. Individuals with **clinical ASCVD**
2. Individuals without clinical ASCVD but with **LDL-C ≥190 mg/dl**.
3. Individuals without clinical ASCVD but **LDL-C 70-189 mg/dl & 40-75 years of age with DM**
4. Individuals without clinical ASCVD or DM, who are 40-75 years of age with LDL-C 70-189 mg/dl, and have an estimated **10-year ASCVD risk of ≥ 7.5%** (identified by **Pooled Cohort Equations** for ASCVD risk prediction)

**NB.**: No recommendations are made to inform treatment decisions in individuals who are not included in the four statin benefit groups.

---

**Pooled Cohort Risk Assessment Equations**

Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event

**Risk Factors for ASCVD**

- Gender: Male, Female
- Age: years
- Race: White, Other
- Total Cholesterol: mg/dL
- HDL Cholesterol: mg/dL
- Systolic BP: mmHg
- Receiving treatment for high blood pressure (if SBP > 120 mmHg): No, Yes
- Diabetes: No, Yes
- Smoker: No, Yes

Reset | Calculate

[http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx](http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx)
ASCVD Statin Benefit Groups

Clinical ASCVD

NO

LDL-C ≥190 mg/dL

YES

High-intensity statin

Age >75 y

Moderate-intensity statin

Age <75 y

NO

DM

YES

ASCVD risk <7.5%

Moderate-intensity statin

ASCVD risk ≥7.5%

High-intensity statin

NO

Age 40-75 y

YES

ASCVD prevention benefit of statin therapy may be less clear

Estimate ASCVD Risk

≥7.5% & age 40-75 y

NO

YES

Moderate-to-high intensity statin

Download from: Google Play Store
Search for: ASCVD Risk
**INDICATIONS FOR HIGH-INTENSITY AND MODERATE-INTENSITY STATIN THERAPY**

- **Indications of High-intensity** (daily dose that lowers LDL-C by ≥50%):
  1. Patients with ASCVD who are age ≤75 years,
  2. Patients with LDL-C ≥190 mg/dL
  3. Diabetics with a 10-year ASCVD ≥7.5%

- **Indications of Moderate-intensity** (daily dose that lowers LDL-C by 30% to <50%).
  - if not a candidate for high-intensity

- **Indications of moderate- to high-intensity:**
  - Persons 40-75 years with a ≥7.5% 10-year ASCVD risk.

NB.: Addition of other cholesterol-lowering agents can be considered to further lower LDL-C.

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL–C by approximately ≥50%</td>
<td>Daily dose lowers LDL–C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C on average, by &lt;30%</td>
</tr>
<tr>
<td><strong>Atorvastatin (40)–80 mg</strong> Rosuvastatin 20 (40) mg</td>
<td>Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg</td>
<td>Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>
(3) NIACIN: [NICOTINIC ACID]

- **Mechanism:** As Fibrates
- **Side effects:**
  1. **Pruritis & flushing**
     - due to release of PGs.
     - Avoided by:
       - aspirin (325 mg).
       - taking with meal,
       - slow titration or
       - use SR formulation (Niaspan)
  2. **Acanthosis nigricans**
  3. **Hyperglycemia** (baseline glu)
  4. **Hyperuricemia** (baseline UA)
  5. **Hepatotoxicity** (baseline LFTs) († when combined with statin)
  6. **GIT disturbances**

**N.B:**
- SR preparations are more hepatotoxic than other preparations but less likely to cause flushing
- **Acipimox (olbitam®):** as niacin with less side effects.

4) BILE ACID BINDING RESINS

- **Examples:**
  - Cholestyramine (Questran)
  - Colestipol (Colestid)
  - Colesevelam (Welchol)

- **Mechanism:**
  - bind with bile acid ➔
    1. ↓ Absorption of cholesterol
    2. ↓ Absorption of bile ➔ ↑ catabolism of cholesterol into bile acids ➔ compensatory ↑ in LDL receptors ➔ ↓ LDL & Cholesterol

- **Indication:**
  - 2nd-line agents when statins not sufficient or not tolerated
  - Potentiate the effect of statins
4) BILE ACID BINDING RESINS (CONTIN.)

Side effects:
1. Constipation
2. Cholesterol gall stones & cholecystitis
3. Counter (decrease) absorption of fat soluble vit. (ADEK) & other drugs e.g.: digoxin & warfarin (Other drugs should be taken 1 hr before or 4 to 6 hrs after resins)

• NB: May aggravate hypertriglyceridemia
  • caution if TG > 200 mg/dL & contraindicated if TG > 400 mg/dL

• NB: FIBBRATES & RESINS

5) EZETIMIBE (ZETIA®):

• Dose: 10 mg PO OD
• Metabolized in liver (not used in advanced liver disease)

• Mechanism:
  • ↓ directly cholesterol absorption
  • ↓ LDL-C ~18 % & has synergistic effect with statin (↓ LDL-C ~ 25 %)

• Uses: Adjunctive therapy to statin
• Monitoring: no monitoring necessary, except LFTs when coadministered with statins
**OMEGA-3 FATTY ACIDS**

- Diets rich in omega-3 FA from oily fish decrease TG & increase HDL
- FDA approved as dietary adjunct (Omacor®, Lovaza®) for very high TG levels (> 500 mg/dL)
- Side effects:
  1. Increase in LDL-C
  2. Thrombocytopenia & bleeding disorders (at more than 3 g/day)

<table>
<thead>
<tr>
<th>Effect on lipids</th>
<th>Effect on lipoproteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>↓ Cholesterol</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>↓ Cholesterol</td>
</tr>
<tr>
<td>Resins</td>
<td>↓ Cholesterol</td>
</tr>
<tr>
<td>Fibrates</td>
<td>↓ Cholesterol, ↓ TG</td>
</tr>
<tr>
<td>Niacin</td>
<td>↓ Cholesterol, ↓ TG</td>
</tr>
</tbody>
</table>
• The ADA IN 2015, has revised its guidelines for use of statins in diabetics to align with ACC/AHA guideline issued in 2013.

• ADA has endorsed the use of statin as ACC/AHA guideline

• Combination therapy (statin/fibrate & statin/niacin) has not been shown to provide additional CV benefit above statin therapy alone & is not generally recommended.

• There is an increased risk of incident DM with statin use, which may be limited to those with diabetes risk factors.
• However, The cardiovascular event rate reduction with statins far outweighed the risk of incident DM even for patients at highest risk for diabetes

<table>
<thead>
<tr>
<th>Reductions</th>
</tr>
</thead>
<tbody>
<tr>
<td>14% ↓ mortality</td>
</tr>
<tr>
<td>27% ↓ CHD (fatal and non fatal) events</td>
</tr>
<tr>
<td>22% ↓ in stroke (fatal and non fatal)</td>
</tr>
<tr>
<td>33% ↓ in nonfatal MI</td>
</tr>
<tr>
<td>38% ↓ in revascularization</td>
</tr>
<tr>
<td>18% ↑ in diabetes</td>
</tr>
</tbody>
</table>
Evidence does not support recommending omega-3 supplements for people with diabetes for the prevention or treatment of cardiovascular events.

PREGNANCY & CHILDREN

- **Pregnancy:**
  - Cholesterol & TG ↑ progressively during pregnancy occurring around the 36th - 39th weeks
  - Drug therapy is not instituted nor is it usually continued during pregnancy.
  - If the patient is very high risk, **resins** may be considered
  - **Ezetimibe** might be an alternative, since it is a Category C drug
  - Statins are category X and are contraindicated.

- **Children:**
  - Drug therapy in children is not recommended until the age of 8 years or older
  - **Resins** were the 1st line treatment, but there is now evidence that **statins** are safe & effective & provide greater lipid lowering.
THANK YOU