Dyslipidemia

- Disorders of the lipid and lipoprotein transport pathways associated with arterial disease
- More appropriate than “hyperlipidemia
  - Low high-density lipoprotein cholesterol (HDL-C) and elevated triglyceride concentrations but average total plasma cholesterol level.
  - Elevated lipoprotein(a)
Certain rare lipoprotein disorders can cause overt clinical manifestations.

Most common dyslipoproteinemias seldom cause symptoms or clinical signs.

Require laboratory tests for detection.

Proper recognition and management of dyslipoproteinemias can reduce cardiovascular and total mortality rates.

### Component of therapeutic life style

<table>
<thead>
<tr>
<th>Component</th>
<th>Recommendations</th>
<th>Approximate LDL reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturated fat</td>
<td>Less than 7% of total calories</td>
<td>8-10%</td>
</tr>
<tr>
<td>Dietary cholesterol</td>
<td>Less than 200 mg/day</td>
<td>3-5%</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>Up to 10% of total calories</td>
<td></td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>Up to 20% of total calories</td>
<td></td>
</tr>
<tr>
<td>Total fat</td>
<td>25-35% of total calories</td>
<td></td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>50-60% of total calories</td>
<td></td>
</tr>
<tr>
<td>Dietary fibers</td>
<td>20-30 gm/day</td>
<td></td>
</tr>
<tr>
<td>Animal protein</td>
<td>15% of total calories</td>
<td></td>
</tr>
<tr>
<td>Therapeutic options of LDL lowering</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plant stanols/sterols</td>
<td>2 g/day</td>
<td>6-15%</td>
</tr>
<tr>
<td>Increased viscous soluble fibers</td>
<td>5-10 gm/day (consumption of 10-25 gm/day may have added benefit)</td>
<td>3-5%</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Enough moderate activity to expend at least 200 Kcal/day</td>
<td></td>
</tr>
</tbody>
</table>
### Lipid reducing drugs

**Statins**
- Niacin
- Bile acid sequestrants
- Fibric acids
- Omega-3 FA
- Ezetimibe

**Other**
- Lomidipide
- Mepomersin
- CETP inhibitors
- PCSK 9 inhibitor
- Recombinant LAL
- Anti apo CIII antisense drug
Statins

Classification

• By manufacture method:
  • Fermentation: Lova, Simva, Prava
  • Synthetic: Fluva, Atorva, Rosuva

• By solubility:
  • Hydrophilic: Prava
  • Lipophylic: Atorva, Fluva, Lova, Simva, Rosu

Statins

Cyp 450 metabolism

• Cyp 3A4: Lova, Simva, Atorva, ceriva

• Cyp 2c9: Fluva

• Cyp 2c9, 2c19: Rosuva
Statins

Net effects

- Decrease LDL-C by up to 35%
- Decrease triglyceride
- Increase HDL-C by up to 10%
- Pleiotropic effect:
  - Anti-inflammatory effect
  - Anti-thrombotic
  - Improve endothelial dysfunction
- Decrease the degree of obstructive atheroma and regress volume of atheroma
- Reduce coronary events, stroke and total mortality

Statins

Drug interaction

- Cyp 3A4 inhibitors:
  - Antifungals, Macrolides, CCB, Protease inhibitors, Grape fruits

- Organic anion transporting peptide inhibitors:
  - Cyclosporin, oral antidiabetics

- Inhibition of glucuronidation:
  - Fibrates (gemfibrozil)
Statin therapy
How to approach

- Treat to a goal:
  - What is the goal?
  - The magnitude of benefit of further LDL lowering?
  - Potential adverse effects

- The lower the better: No evidence

- Life time risk: No long term follow up study (> 15 years)

- Treat the level of ASCVD risk: Extensive body of evidence

Indications for statin therapy
Body of evidence

2010 Meta-analysis (21 trials with > 129.000 participant):

**Efficacy**
- One mmol/L decrease in LDL associated with:
  - 25% decrease in vascular event
  - 10% decrease in all cause mortality
- Similar effect in trials comparing statin vs. placebo
  and high intensity statin vs. low intensity statin
- All subgroups similar magnitude of risk reduction
- No effect modification regarding baseline LDL level

**Safety**
- Side effects: No increase in cancer or death from non-vascular cause
Indications for statin therapy
Body of evidence

2012 Meta-analysis:

- Benefits associated with statin at least as impressive in primary prevention as in secondary prevention

- The relative risk reduction was larger in primary prevention among patient at lowest absolute risk

- Ever earlier therapy over life time risk may be the best biological way to handle elevated cholesterol level

Indications for statin therapy

Four major benefit groups:

- Secondary prevention in **patients with ASCVD**

- Primary prevention:
  - LDL > 190 mg/dL
  - Diabetic patients (LDL 70-189 mg/dL)
  - High near term risk for ASCVD, (LDL 70-189 mg/dL)
Indications for statin therapy

- In selected individual additional risk factors should be looked for:
  - LDL > 160 mg/dL
  - FH of premature ASCVD
  - CAC > 300 units Agatston or > 75th percentile
  - Hs CRP > 2 mg/dL
  - ABI < 0.9
  - Life time risk

Indications for statin therapy

Decision for statin therapy to prevent ASCVD is a balance between
The potential for benefit and risk from statin therapy
Incorporating patient preference
Statins

Side effects

- Gastrointestinal disturbances
- Muscle injury: myositis, myopathy, rhabdomyolysis
- Liver injury: transaminitis, hepatitis, cholestasis, autoimmune liver injury
- Diabetes mellitus
- Acute kidney injury
- Sleep problems
- Hemorrhagic stroke (1/10000 cases)
- Memory loss
- Erectile dysfunction

Statins

Muscle safety

- Obtain baseline CK (patient at risk)
- Obtain CK if muscle symptoms develop
- Muscle symptoms
  (weakness, fatigue, pain, tenderness, cramps, stiffness)
**Muscle symptoms**

- Severe and unexplained
  - DC Serum creatinine Urine analysis
- Mild or moderate
  - DC Wait until resolution of symptoms and assess conditions that cause muscle symptoms

**Symptoms resolved**
- Re-challenge to establish causal relation
  - And if causal relation exist shift to other statin
- More than 2 months off statin with persistent symptoms or CK elevation
  - Assess for other cause

**Statins**

**Liver injury**

- Obtain ALT and when clinically indicated (not routinely) during the course of treatment
- If ALT < 3X ULN: continue (it usually drop)
- DC statin if ALT > 3 X ULN, hyperbilirubinemia and serious liver injury
Statins

Diabetes mellitus

- 1/1000 cases per year (moderate intensity)
- 3/1000 cases per year (high intensity)
- Most of them have IFG
- Long term adverse effect of statin associated DM unlikely to be equivalent to a MI, non-fatal stroke or death (NNT vs. NNH)

Statins

Management of intolerance

- R/O factors that increase the risk of myopathy or hepatic injury
- Switching therapy (Fluvastatin or Pravastatin)
- Alternate day dosing (not the optimal)
- Non-statin lipid lowering drugs
- Lipid lowering nutraceuticals: red yeast rice (similar to lovastatin, less potency and contaminant)
- Specific therapy: Co Q 10 (lack of benefit in small clinical trials) and Vit. D (marker of other nutritional deficiencies)
Statins

Proness to intolerance

- Age > 75
- Impaired liver and renal functions
- Concomitant drugs that affect statin intolerance

Ezetimibe

Mechanism of action

- Inhibit cholesterol absorption from intestine (bruch border) by binding to the protein product of the Neiman-Pick C1 like 1 gene
Ezetimibe

Net effects

- Reduce LDL-C (15-20%)
- Metabolized by liver and intestine by glucuronide conjugation (not p450)
- Few drug interaction (cyclosporins, fibric acid and warfarin)
- Not recommended in severe hepatic dysfunction
- Improvement of CV outcomes: IMPROVE IT trial

Proprotein convertase subtilisin/ Kexin type 9 (PCSK 9) inhibitors

- **Preparations**: Evolocumab (Repatha®), Alirocumab (Praluent®)
- Inhibition of circulating PCSK 9 allows **recycling of LDL receptors**
- Statins increase PCSK 9 limiting the effects of increasing doses
- Lower LDL-C by 40-70%, decrease Lp(a) significantly
- **Adverse reactions**: injection site reactions, upper respirator tract infections, myalgia
- Long term outcome results: unavailable
**PCSK9 Mechanism of Action**

LDL degradation and recycling of LDL-R


**PCSK9 has functional effects on LDL-receptor protein**

SREBP-2

PCSK9 inhibitor
Bile acid sequestrants

Preparations

- Cholestipol: rarely used because of interaction with cardiovascular drugs and Vit. K
- Cholestyramine: powder and pills
- Colesevelam: granules and tablets
  - Less costipating
  - Does not adsorb vitamins
  - Does not raise TG

Mechanism of action

- Block inhibitory effect of bile acids absorbed from gut on 7 α hydroxylase leading to depletion of hepatocytes cholesterol and upregulation of LDL receptors
- Increase HDL by upregulation of the gene encoding ABC transport protein A1 (normally inhibited by bile acids)
- Decrease LDL by 15-25%
- Slight increase in triglycerides
- Insignificant effect on HDL
- Colesevelam (and other resins) lowers HB A1C by 5%
Bile acid sequestrants

Side effects

- Constipation and indigestion
- Runny nose, sore throat
- Weakness and fatigue
- Muscle pain

Use with caution

- If baseline TG > 250-299 mg/dL and discontinue if it > 400 mg/dL
- FBG before initiation and during follow up

Contraindications

- If baseline TG > 300 mg/dL or type III hyperlipoproteinemia
Fibric acids

Preparations

- Gimfibrozile
- Fenofibrate
- Bezofibrate
- Ciprofibrate

Mechanism of action

- Activates PPAR-α: increase beta oxidation of FA in the liver decrease VLDL secretion and increase clearance of chylomicrons
- Increase LPL and decrease apo C III
- Enlarge LDL particle size; less oxidation and increase affinity to the receptors
- Increase HDL-C
Fibric acids

**Net effects**

- Decrease TG (40%) and LDL-C (10-15%)
- Increase HDL-C (15-20%)
- Interfere with glucoronidation of statins (except pitovastatin and fluvastatin)
- Bound to albumin so displacing other drugs (e.g. warfarin)
- 60-90% renally excreted
- Should be avoided in pregnancy
- Reduction of cardiovascular events: uncertain

**Safety**

- Avoid Gemfibrosil with statin
- May be considered with low or intermediate intensity stain if Benefit > risk
- Evaluate of renal function (serum creatinine and eGFR before initiation and the every 6 months)
  - Avoid if GFR < 30 ml/min per 1.73m²
  - GFR 30-59 ml/min per 1.73m²; Fenoferbate should not exceed 54 mg/d
  - GFR persistantly < 30 ml/min per 1.73m² during follow up; Discontinue
Management of Hypertriglyceridemia

- TG ≥ 1000 mg/dL or ≥ 500 mg/dL with prior pancreatitis
- Prior CVD/stroke/PAD or DM or LDL ≥ 190 mg/dL or 10 yr risk ≥ 7.5% and age > 40 and LDL > 70 mg/dL
  - Control DM
  - Statin + Fenofibrate
  - Adjust meds
  - Counsel alcohol cessation
- Isolated TG
  - Low fat diet
  - Adjust Meds
  - Counsel alcohol cessation
  - Start Gemfibrozil or Fenofibrate

Omega-3 fatty acids

Preparations

- Eicosapentaenoic acid (EPA) (Vascepa)
- Docosahexaenoic acid (DHA)
- (Vovaza = EPA + DHA)
Omega-3 fatty acids

Mechanism of action

- Increase fatty acids oxidation in hepatocytes
- Increase apo B degradation thus decreasing hepatic VLDL secretion
- Reduce hepatic production of VLDL by inhibiting diglycerol acyl transferase
- Increase lipoprotein lipase activity
- Increase chylomicrons clearance

Net effects

- Recommended for hypertriglyceridemia (FDA approved)
- Value in improving cardiovascular outcome: uncertain
- Safety in patients allergic to sea food: undetermined
Omega-3 fatty acids

**Precautions**

- GI disturbances
- Skin changes
- Bleeding

**Niacin**

**Preparations**

- Immediate release e.g. Niacor: more flushing and less hepatotoxicity
- Extended release e.g. Niaspan: less flushing and more hepatotoxicity
- Long acting e.g. Enduracin
G protein coupled receptor

- Side effects
- AIM HIGH
- Value of raising HDL level?

- This drug should be considered obsolete; its use not justifiable yet continues to be prescribed (M. Gabriel Khan, Cardiac drug therapy, 8th edition)
Cholesterol Ester Transfer Protein (CETP) Inhibitors

- Multi-decade Framingham Heart Study (since 1997) suggested that having high HDL could be more cardioprotective than having low cholesterol
- These oral drugs were the first to provide dramatic HDL elevation – more than doubling a person’s levels
- Expectations for the CETP class of drugs were sky high

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Cholesterol Ester Transfer Protein (CETP) Inhibitors

- Preparations: Torcetrapib, Dalcetrapib, Evocetrapib and anacetrapib
- Pharmacological increase in HDL-C may not decrease cardiovascular risk
- Torcetrapib increase blood pressure, decrease serum K, increase aldosterone and increases cardiac events and mortality (off target effect)
- Dalcetrapib, Evocetrapib: no clinical benefit
- Anacetrapib (Define study, Reveal study)
- TA-8995 — novel inhibitor or CETP, raised HDL-C levels and lowered LDL-C levels significantly without evidence of serious side effects in the TULIP trial)
• Genetic analysis failed to show a causal association between genetically raised plasma HDL-cholesterol (HDL-C) levels and risk of myocardial infarction
• Recent large-scale clinical trials have failed to demonstrate a clinical benefit of HDL-C-raising therapies when added to standard therapy
• Although the HDL cholesterol hypothesis may be defunct, the HDL function hypothesis is now poised to be rigorously tested.

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**Lomidipide**

• Block microsomal triglyceride transfer protein (MTTP), thus decreases lipid input into lipoproteins (increase liver fat by 10%)
• Approved for treatment of homozygous familial hypercholesterolemia
• Side effects mainly gastrointestinal, ALT and AST elevation
• Very expensive
**Mipomersin**

- Antisense oligonucleotides that binds to mRNA to prevent apo B synthesis (inhibit of protein translation), thus inhibits apo B containing lipoprotein synthesis
- Approved for treatment of homozygous hyperlipidemia
- Side effects: injection site reactions, hepatic steatosis and necrosis, angina and AMI

**Apo CIII Antisense Drug**

- Blocks the LPL inhibitory effects of apo CIII
- Reduces TG by 81% and increases HDL-C by 78%
- Used for familial chylomicronemia
- Adverse effects: injection site reactions
Do not use

- **Niacin**: ALT > 3 ULN, severe cutaneous symptoms, persistent hyperglycemia, acute gout, recent onset AF and weight loss
- **Bile acid sequestrants**: TG > 300 mg/dL, type III hyperlipoproteinemia
- **Fibrates**: statin + gemfibrozile, Fenofibrate if GFR < 30 ml/min
- **Ezetimib**: ALT > 3 ULN

**LDL Apheresis**

- Homozygous FH
- Heterozygous FH
  - Failed 6 months of diet and drug therapy
  - LDL > 300 mg/dL
  - LDL > 200 mg/dL with CAD
LDL Apheresis

Methods

- Dextran sulphate LDL adsorption (liposorber)
- Heparin induced LDL precipitation (HELP system)

LDL Apheresis

Efficacy

- 70% reduction of LDL per session
- 1-2 sessions/ week
- Interval mean LDL reduction should be 60%
- Well tolerated
- Some patients show progression of cardiovascular disease
Thank You