Introduction:

- Fat (lipids) are combinations (esters) of fatty acids plus an alcohol. The two main fats in the body are triglycerides (TGs) and cholesterol.
- **Triglycerides** (glycerol esterified with 3 fatty acids), normal level is < 150 mg/dL (1.69 mmol/L) and high value is above 200 mg/dL (5.17 mmol/L).
- Triglycerides (TGs) are esters made from glycerol and 3 long-chain fatty acids. They are used for energy and the formation of skin oils.
- TGs are typically carried by very low-density lipoproteins and chylomicrons, which are formed in the small intestine after the ingestion of dietary fat and cholesterol.
- **Cholesterol** (cholesterol alcohol esterified with fatty acids), normal value is < 200 mg/dL (5.17 mmol/L).
- Cholesterol and fats are carried in the bloodstream inside of lipoproteins, hydrophobic spheres that transport lipophilic substances through the body.
- Cholesterol, triglycerides, and phospholipids are transported as complexes of lipids and specialized proteins (apolipoproteins) known as lipoproteins.
- **Chylomicrons** are large lipoprotein particles that are created by the absorptive cells of the small intestine. Chylomicrons transport lipids to adipose tissue where they are broken down by lipoprotein lipase.
- The 3 routinely monitored lipoproteins are as follows: very-low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). **LDL-C contains mostly cholesterol**, which it transports from the liver to the periphery.
- Similar to LDL-C, HDL-C is mostly cholesterol, but it carries cholesterol from the periphery to the liver, a process called reverse cholesterol transport.
- **Very Low Density Lipoprotein (VLDL)** is a lipoprotein subclass. It is assembled in the liver from cholesterol and apolipoproteins. It is converted in the bloodstream to low density lipoprotein (LDL). **VLDL is prone to accelerate atherosclerosis**, and is elevated in a number of diseases and metabolic states. Target value is > 60 mg/dL.
- **Low-density lipoprotein (LDL)** refers to a class and range of lipoprotein particles, which carry cholesterol in the blood and around the body, for use by cells. It is the final stage of VLDL. Normal value is < 100 mg/dL.
- **LDL-C is the primary target for lipid-lowering therapy** and the treatment goals for LDL-C levels are based on cardiovascular disease (CVD) event risk stratification.
- Total cholesterol (TC) levels are comprised of HDL-C, LDL-C, and TG (TC=HDL-C+LDL-C+ VLDL/5).
- **High-density lipoprotein (HDL)** is “bad cholesterol”. HDLs are the smallest of the lipoproteins. Low concentrations of HDL (below 40 mg/dL or 1.03 mmol/L for men, below 50 mg/dL for women) are a positive risk factor for these atherosclerotic diseases. High levels of HDL-C reduce the risk of atherosclerosis.
- Dyslipidemia is a modifiable yet highly prevalent risk factor for atherosclerotic disease and its complications, including coronary heart disease (CHD), myocardial infarction (MI), stroke, peripheral vascular disease, and cardiac death.
- Among adults in the United States, 16.2%, or 35.7 million people, have serum total cholesterol (TC) levels ≥240 mg/dL, and 25.3% of adults have low-density lipoprotein cholesterol (LDL-C) levels ≥160 mg/dL.
- Dyslipidemia management typically focuses on controlling elevated LDL-C levels based on guideline recommendations, with a secondary focus on correcting other lipid levels such as non–high-density lipoprotein cholesterol (non–HDL-C), HDL-C, and triglycerides (TGs).
- In the landmark INTERHEART study, abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, and sedentary lifestyle accounted for more than 90% of the worldwide risk of MI.
- A more recent analysis of INTERHEART focused on specific lipid parameters, including plasma lipids, lipoproteins, and apolipoproteins as indices of MI risk.
- Growing evidence indicates that lipoproteins other than LDL-C play an important role in atherogenesis, atherosclerotic vascular disease, and CV morbidity and mortality.
- The fasting apolipoprotein B100 (ApoB)/apolipoprotein A1 (ApoA1) ratio was a better predictor of MI risk than other candidate markers, including LDL-C/ HDL-C and TC/HDL-C.
- In several other trials, HDL-C, non–HDL-C, and ApoB abnormalities have outperformed LDL-C as predictors of CVD and adverse CV events.

Nonpharmacological treatment:

- **Smoking cessation**
- Take antioxidant vitamins (A, C, E). Long term, high doses may slow atherogenesis.
- Diet modifications (reduction in fats, proteins and carbohydrates), eat homemade food if possible. Trans-fatty acids, found in bakery shortening and stick margarine, are especially linked to increased TG levels.
- Moderate exercise 30 minutes 5 times per week or 10000 steps every day. A 5% to 10% weight loss can decrease TG by 20%.
- **Avoid alcohol**
Fish oils are rich in omega 3 polyunsaturated fatty acids (linolenic acid). They decrease the synthesis and enhance clearance of VLDL. These are as effective as vegetable oils (omega 6 fatty acids) in controlling lipids (TGs).

A Mediterranean diet, which is comprised of foods high in monounsaturated, polyunsaturated fat, and fiber, is associated with lower TG levels. A Mediterranean-type diet has been shown to be more effective than a low-fat diet for reducing TG levels.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C (mg/dL)</th>
<th>Non-HDL-C (mg/dL)</th>
<th>ApoB (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest risk patients, defined as those with Known CVD</td>
<td>&lt;70</td>
<td>&lt;100</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Diabetes plus 1 additional major CVD risk factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk patients, defined as those with No diabetes or known clinical CVD but ≥2 additional Major CVD risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes but no other major CVD risk factors</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

Risk factors:
- Cigarette smoking
- Hypertension (blood pressure ≥140/90 mm Hg or on antihypertensive medication)
- Low HDL-C (<40 mg/dL)
- Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)
- Age (men ≥45 years; women ≥55 years).
- 10-year risk for CHD: estimated risk for “hard” CHD outcomes, including MI and coronary death, based on data from the Framingham Heart Study using age, gender, cigarette smoking, TC, HDL-C, systolic blood pressure, and treatment for hypertension as risk factors.

Life Style Modifications for Dyslipidemia:

<table>
<thead>
<tr>
<th>Life Style Component</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet Considerations</td>
<td></td>
</tr>
<tr>
<td>Saturated fats</td>
<td>&lt;7% of total calories</td>
</tr>
<tr>
<td>Dietary cholesterol</td>
<td>≤200 mg/d</td>
</tr>
<tr>
<td>Plant stanol/sterols</td>
<td>2 g/d</td>
</tr>
<tr>
<td>Viscous (soluble) fiber</td>
<td>10 to 25 g/d</td>
</tr>
<tr>
<td>Total calories (energy)</td>
<td>Adjust to maintain desirable body weight/prevent weight gain</td>
</tr>
</tbody>
</table>
Physical moderate exercise | Enough moderate exercise to expend ≥200 kcal/d

Drug Therapy

Statins:
- Inhibit HMG – CoA reductase, interrupting the conversion of HMG – CoA to mevalonate involved in liver cholesterol biosynthesis.
  - Inhibition of this enzyme halts the liver’s biosynthesis of cholesterol. Since the liver requires cholesterol for hormone synthesis, a reduction in serum cholesterol levels causes the liver to increase the number of LDL-C receptors on the surface of hepatocytes, which increases cholesterol uptake from the serum. Currently there are 7 HMG-CoA reductase inhibitors marketed.
- Statins are primarily used to reduce LDL-C levels, but higher doses of atorvastatin, rosuvastatin, and simvastatin substantially lower TG levels, as well.

<table>
<thead>
<tr>
<th>Name and Dose</th>
<th>Efficacy</th>
<th>Adverse Effects</th>
<th>Interactions</th>
<th>Precautions/Comments/Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin (Lipitor) 10 – 80 mg po QD</td>
<td>Most effective Greater effect on lowering LDL (50%) and TC (30%)</td>
<td>GI effects Myositis Elevated LFTs Constipation occurs in fewer patients</td>
<td>Metabolized by 3A4: Atorvastatin Simvastatin Lovastatin</td>
<td>Absolute contraindicated in pregnancy and lactation Adjust dose in severe renal impairment Can be used with bile acid resins Pravastatin is least protein bound Atorvastatin and rosuvastatin can be taken at any time while the rest at evening time or bed time Grape fruit juice should be avoided. LFTs q 3 months and CPK Limit alcohol consumption Evaluate muscle symptoms and CK initially. Evaluate muscle symptoms at each follow-up visit. Obtain a CK when patient has muscle soreness, tenderness, or pain.</td>
</tr>
<tr>
<td>Lovastatin (Mevacor) 20 – 80 mg po QD with food</td>
<td>Most effective Greater effect on lowering LDL (50%) and TC (30%)</td>
<td>GI effects Myositis Elevated LFTs Constipation occurs in fewer patients</td>
<td>Metabolized by 3A4: Atorvastatin Simvastatin Lovastatin</td>
<td>Absolute contraindicated in pregnancy and lactation Adjust dose in severe renal impairment Can be used with bile acid resins Pravastatin is least protein bound Atorvastatin and rosuvastatin can be taken at any time while the rest at evening time or bed time Grape fruit juice should be avoided. LFTs q 3 months and CPK Limit alcohol consumption Evaluate muscle symptoms and CK initially. Evaluate muscle symptoms at each follow-up visit. Obtain a CK when patient has muscle soreness, tenderness, or pain.</td>
</tr>
<tr>
<td>Simvastatin (Zocor) 10 – 40 mg po qhs</td>
<td>Most effective Greater effect on lowering LDL (50%) and TC (30%)</td>
<td>GI effects Myositis Elevated LFTs Constipation occurs in fewer patients</td>
<td>Metabolized by 3A4: Atorvastatin Simvastatin Lovastatin</td>
<td>Absolute contraindicated in pregnancy and lactation Adjust dose in severe renal impairment Can be used with bile acid resins Pravastatin is least protein bound Atorvastatin and rosuvastatin can be taken at any time while the rest at evening time or bed time Grape fruit juice should be avoided. LFTs q 3 months and CPK Limit alcohol consumption Evaluate muscle symptoms and CK initially. Evaluate muscle symptoms at each follow-up visit. Obtain a CK when patient has muscle soreness, tenderness, or pain.</td>
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<td>Fluvastatin (Lescol) 20 – 80 mg po qhs</td>
<td>Most effective Greater effect on lowering LDL (50%) and TC (30%)</td>
<td>GI effects Myositis Elevated LFTs Constipation occurs in fewer patients</td>
<td>Metabolized by 3A4: Atorvastatin Simvastatin Lovastatin</td>
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<td>Rosuvastatin (Crestor) 10 – 40 mg po qd</td>
<td>Rosuvastatin has greatest decrease in LDL and atorvastatin is most effective in decreasing TGs Increasing dose will not provide much increasing effect</td>
<td>Lovastatin and simvastatin are prodrugs and require liver hydrolysis Stabilize plaques in MI patients</td>
<td>Metabolized by 3A4: Atorvastatin Simvastatin Lovastatin</td>
<td>Absolute contraindicated in pregnancy and lactation Adjust dose in severe renal impairment Can be used with bile acid resins Pravastatin is least protein bound Atorvastatin and rosuvastatin can be taken at any time while the rest at evening time or bed time Grape fruit juice should be avoided. LFTs q 3 months and CPK Limit alcohol consumption Evaluate muscle symptoms and CK initially. Evaluate muscle symptoms at each follow-up visit. Obtain a CK when patient has muscle soreness, tenderness, or pain.</td>
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<tr>
<td>Pravastatin (Pravachol) 10 – 40 mg po qhs</td>
<td>Lovastatin and simvastatin are prodrugs and require liver hydrolysis Stabilize plaques in MI patients</td>
<td>Metabolized by 3A4: Atorvastatin Simvastatin Lovastatin</td>
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<td></td>
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<tr>
<td>Pitavastatin (Livalo) 1 – 4 mg qhs</td>
<td>Lovastatin and simvastatin are prodrugs and require liver hydrolysis Stabilize plaques in MI patients</td>
<td>Metabolized by 3A4: Atorvastatin Simvastatin Lovastatin</td>
<td>Absolute contraindicated in pregnancy and lactation Adjust dose in severe renal impairment Can be used with bile acid resins Pravastatin is least protein bound Atorvastatin and rosuvastatin can be taken at any time while the rest at evening time or bed time Grape fruit juice should be avoided. LFTs q 3 months and CPK Limit alcohol consumption Evaluate muscle symptoms and CK initially. Evaluate muscle symptoms at each follow-up visit. Obtain a CK when patient has muscle soreness, tenderness, or pain.</td>
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Serum Cholesterol Absorption Inhibitor: inhibits intestinal absorption of cholesterol and related phytosterols.

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<tr>
<td>Ezitimibe (ezetrol) 10 mg po QD</td>
<td>Well tolerated and can be taken any time Can be used with statins ↓17.7% serum LDL – C, ↑11.3% serum HDL – C, ↓5.7% serum TGs In patients who do not achieve target LDL-C levels with statin therapy alone, combination therapy with ezetimibe and a statin may provide additional LDL-C–lowering, but its effect on CV outcomes is controversial</td>
<td>Diarrhea fatigue Not significant</td>
<td>Should be taken 2 hr before or 4 hours after antacids</td>
<td></td>
</tr>
</tbody>
</table>

Bile acid resins:
- bind to bile acids in the intestinal lumen interrupting the enterohepatic circulation of bile acids, which decreases the bile acid pool size and stimulates hepatic synthesis of bile acids from cholesterol.
- Bile acid sequestrants are resins that reduce serum cholesterol levels by increasing the elimination of cholesterol-rich bile, which in turn increases hepatic bile production.
- Serum LDL-C levels are decreased because the liver has to increase uptake of cholesterol from the blood to increase bile acid production. There are 3 bile acid sequestrants that are FDA approved – cholestyramine, colestipol, and colesuvelam.
Not routinely used to treat TGs.

<table>
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| Cholestyramine (Questran)   | Cholestyramine: 4 – 24 g/d 1 – 2 hour before meals                              | Flatulence                    | Decreases absorption of fat soluble vits (A, D, E, K) | Safe in pregnancy  
|                             | Colestipol: 5 – 30 g/d 15 to 30% reduction in LDL and TC                         | Bloating, Nausea, Constipation | A lot of interactions with many drugs and decrease absorption mainly by adsorption | Take 1 hr before or 4 hours after any other medication  
|                             | no effect on HDL can be used with statins and fibrates and in increased TGs levels | No absorption                 |                                                    | High fiber diet is recommended to decrease constipation  
|                             | Peak effects are seen after 3 weeks.                                             |                               |                                                    | Colestipol is tasteless and odourless  
|                             |                                                                                  |                               |                                                    | Tab form has better palatability  
| Colesevelam                 |                                                                                  |                               |                                                    | Vitamin A, D, E, K supplement may be required on long term          |

**Fibric acids (Fibrates):**
- Act on VLDL, decrease hepatic cholesterol synthesis and increase LDL catabolism
- There are 2 fibric acid derivatives (fibrates) that are available and these are gemfibrozil and fenofibrate
- They primarily reduce VLDL-C through a very complex mechanism. Fibrates activate peroxisome proliferator-activator receptor-alpha (PPAR-α), which increases hepatic oxidation of fatty acids; decreases TG secretion from the liver, increases VLDL-C clearance by increasing lipoprotein lipase activity, and increases clearance of remnant particles, preventing them from being converted to VLDL-C.
- Additionally, fibrates increase HDL-C levels because they increase the genes that code for important HDL-C proteins. In addition, they increase the affinity of the liver's LDL-C receptors and, as a result, they enhance hepatic clearance of LDL-C and lower serum LDL-C levels

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</table>
| Bezafibrate (Bezalip SR) 200 mg po TID with meals | Second line to statins, have greatest effect on lowering TGs (20 to 55%) Good for diabetics | Nausea Abdominal pain Fatulence Rash Insomnia Myalgia Rhabdomylosis | Statins Warfarin Oral coagulants level increases | Gemfibrozil increase stone formation  
| Fenofibrate 100 mg po BID – QID with meals | First gen. (gemfibrozil) cause an increase in mortality and LDL Modest increase in HDL – C (10% - 35%) and decrease in LDL – C (5 – 20 %) Bezafibrate and fenofibrate are most effective for patients with elevated LDL-C levels and mixed dyslipidemia. |                                                   |                                                       | Clofibrate is obsolete now  
| Fenofibrate microcoated (Lipid supra) 160 – 200 mg po QD with main meal | Bezafibrate and fenofibrate are most effective for patients with elevated LDL-C levels and mixed dyslipidemia. |                                                   |                                                       | Contraindicated in pregnancy and lactation  
| Fenofibrate micronized (Lipidil micro) 200 mg po QD with main meal | Patients with atherogenic dyslipidemia benefit from combination therapy with niacin and fibric acid derivatives. |                                                   |                                                       | Precaution in renal failure  
| Gemfibrozil (Lopid) 600 mg BID 30 mins. ac meal |                                                   |                                                   |                                                       | Ok to use in hepatic failure |

**Nicotinic Acid:**
- Reduces the hepatic synthesis of VLDL, cause a reduction in the synthesis of LDL and increases HDL by reducing its catabolism.
Niacin blocks adenylate cyclase in adipocytes, which blocks lipolysis and decreases TG levels. Hepatic production of VLDL-C decreases because less fatty acid is extracted from adipose tissue. Niacin increases serum HDL-C levels by inhibiting the uptake of HDL-C by the liver, but does not attenuate the removal of cholesterol from HDL-C.

This results in an increased circulating HDL-C level available to take cholesterol from the periphery to the liver. Niacin also reduces lipoprotein-A, which has been shown to correlate with CHD risk.

### Prescription Omega 3 fatty acids:
- Regular consumption of fish, dietary supplementation with fish oils rich in omega-3 fatty acids, or use of prescription-strength omega-3 fatty acid can correct elevated TG levels.
- Specifically, omega-3 fatty acids reduce the secretion of TG-rich lipoproteins from the liver, and therefore may be particularly effective in managing patients with hypertriglyceridemia.
- High-dose omega-3 fatty acids (0.9 g/d eicosapentaenoic acid [EPA] + docosa-hexaenoic acid [DHA]) appear to reduce the risk of major coronary events. Usual dose is 1 gram four times a day.
- Lovaza 4 g per day and Vascepa 4 g per day is equally effective. Lovaza reduces 45% TGs, increase LDL by 45%, decreases TC by 9% and increases HDL by 9%.

### Recommendations to Health Professionals Regarding the Liver and Statin Safety:
- Obtain liver transaminase levels before starting therapy.
- Measure transaminase levels 12 weeks after initiating therapy, after a dose increase, and periodically thereafter. However, routine monitoring is not supported by the available evidence and the current recommendation for monitoring needs to be reconsidered by the national guidelines.
- Alert patients to report symptoms of potential hepatotoxicity. Evidence for hepatotoxicity includes jaundice, hepatomegaly, increased indirect bilirubin level, and elevated prothrombin time. Fractionated bilirubin is a more accurate prognosticator of liver injury than isolated aminotransferase levels.
- If objective evidence of significant liver injury, the statin should be discontinued.
- If an isolated asymptomatic transaminase level is 1-3 x ULN, there is no need to discontinue the statin.
- If an isolated asymptomatic transaminase level is >3 x ULN, repeat the test; if still elevated, other etiologies should be ruled out. Consideration should be given to continuing the statin, reducing its dose, or discontinuing it based on clinical judgment.
- Patients with chronic liver disease, nonalcoholic fatty liver disease, or nonalcoholic steatohepatitis may safely receive statin therapy.

### Recommendations to Health Professionals Regarding the Muscle and Statin Safety
- Whenever muscle symptoms or an increased CK level is encountered in a patient receiving statin therapy, health professionals should attempt to rule out other etiologies, because these are most likely to explain the findings. Other common etiologies include increased physical activity, trauma, falls, accidents, seizure, shaking chills, hypothyroidism, infections, polymyositis, dermatomyositis, alcohol abuse, and drug abuse (cocaine, amphetamines, heroin, or phencyclidine).

### Table: Niacin (Nicotinic acid) Dose and Efficacy

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Niacin (Nicotinic acid)</td>
<td>500, 1000 mg tabs/caps</td>
<td>Vitamin B3 Adult: 250 – 1500 mg po BID with food 20 % reduction in LDL and TC Provides greatest increase in HDL (20%) Good decrease in TGs (up to 50%)</td>
<td>PG mediated facial flushing and rash Orthostatic hypotension Hyperuricemia (inhibits uric acid excretion) Myopathy GI intolerance</td>
<td>Increases effects of hypoglycemia With statins / fibrates cause more myopathy Cutaneous flushing and itching can be prevented by taking ASA 325 mg 30 minutes before niacin Titrate dose slowly upward Blood glucose, LFTs, pretreatment and every 6 – 12 weeks for first year then periodically. Lipid profile periodically. Concomitant use of alcohol and hot drinks may magnify pruritus Caution in liver disease, diabetes and gout. Obtain an ALT/AST initially, 6-8 weeks after reaching a daily dose of 1500 mg, 6-8 weeks after reaching the maximum daily dose, then annually or more frequently if indicated. Obtain an FBG and uric acid initially, 6-8 weeks after starting therapy, then annually or more frequently if indicated to monitor for hyperglycemia and hyperuricemia.</td>
</tr>
</tbody>
</table>

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• Obtaining a pretreatment, baseline CK level may be considered in patients who are at high risk of experiencing muscle toxicity (e.g., older individuals; patients receiving combination statin plus agent known to increase myotoxicity), but this is not routinely necessary in other patients.

• **Patients receiving statin therapy should be counseled about the increased risk of muscle complaints**, particularly if the initiation of vigorous, sustained endurance exercise or a surgical operation is being contemplated; they should be advised to report such muscle symptoms to a health professional.

• In patients who **develop tolerable muscle complaints or are asymptomatic with a CK <10 ULN, statin therapy may be continued** at the same or reduced doses and symptoms may be used as the clinical guide to stop or continue therapy.

• In patients who **develop rhabdomyolysis** (CK >10,000 IU/L or CK >10 × ULN with an elevation in serum creatinine or requiring IV hydration therapy), **statin therapy should be stopped**. IV hydration therapy in a hospital setting should be instituted if indicated for patients experiencing rhabdomyolysis. Once recovered, the risk versus benefit of statin therapy should be carefully reconsidered.