# Dyslipidemia

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Pharmacotherapy I

# Learning Objectives

| | |
|---|---|
| Describe | • Describe the pathophysiology of dyslipidemia and its correlation with coronary heart disease |
| Assess | • Assess patient factors to determine intensity of treatment for hyperlipidemia |
| List | • List primary effects on the lipid profile for each class of lipid medications |
| Recommend | • Recommend appropriate pharmacotherapy for lipid disorders |
| Counsel | • Counsel patients on dyslipidemia therapy and lifestyle modifications |

# Background

Ischemic heart disease and cardiovascular heart disease = leading cause of morbidity and mortality

Over 30 YO: total CHO > 260mg/dL = 33% risk of death, total CHO

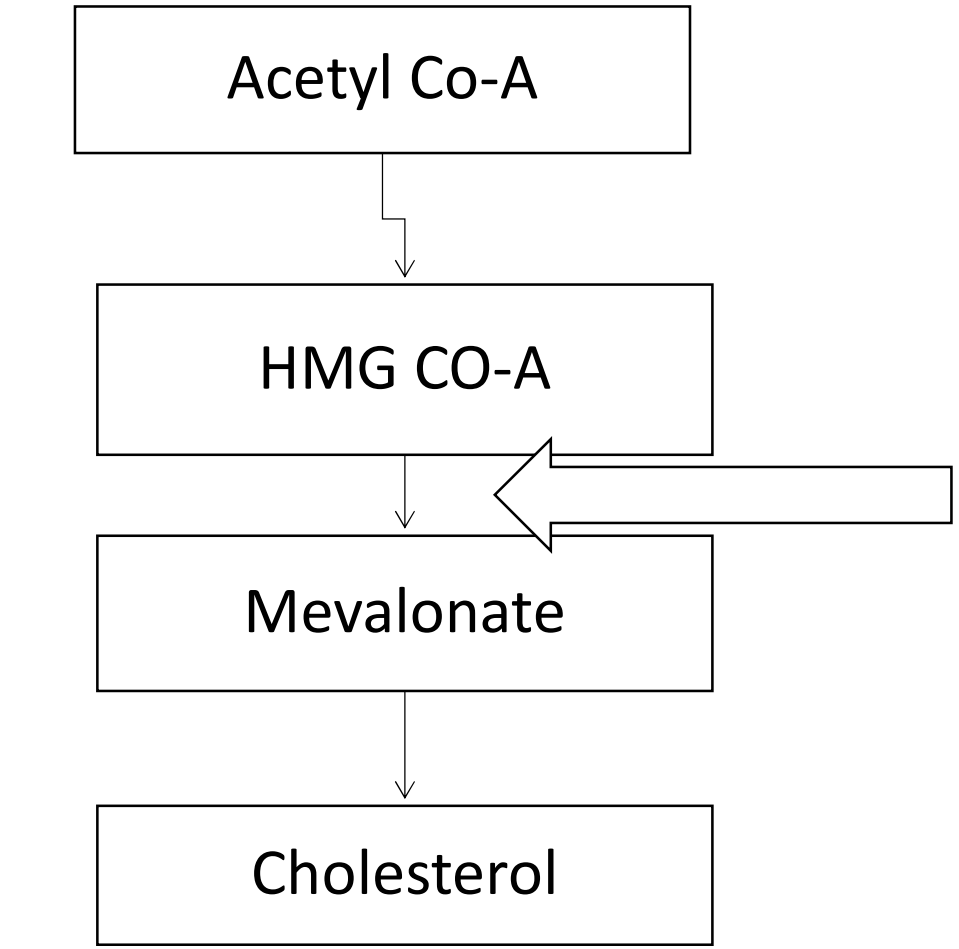
- < 180mg/dL = 15% risk of death

Millions of adults have CHO ≥ 200mg/dL

Millions of adults have CHO ≥ 240mg/dL

Every day about 2500 Americans die from CVD (avg: 1 death every 35 seconds)

# Cholesterol Synthesis




HMG CO-A Reductase
(rate limiting step)

# Definitions

## Cholesterol

- Waxy, fat-like substance
- Synthesized by the liver

## Triglycerides

- Storage form of fat
- Three fatty acids + glycerol

## Circulate as lipoproteins

- Very low-density lipoproteins (VLDL)
- Low density lipoproteins (LDL)
- High density lipoproteins (HDL)

# Classes of Lipoproteins

## Very-low density lipoprotein (VLDL)

- 10 to 15% of total serum cholesterol
- Triglyceride-rich lipoproteins
- Produced by liver Precursors of LDL
- VLDL remnants  appear to promote  atherosclerosis

## Intermediate-density lipoprotein (IDL)

- Derived from VLDL in capillaries of adipose tissue & muscle
- Major lipid component: endogenous cholesterol (CHO > TG)

# Classes of Lipoproteins

Low Density Lipoprotien lousy or " Bad" cholesterol

- Makes up 60 to 70% of total serum cholesterol
- Derived from VLDL
- One of the major atherogenic lipoproteins
- Identified as primary target of cholesterol- lowering therapy
- Every LDL drop by 39mg/dl 21% ↓ major vascular events
- Every 1%↓ LDL 1% ↓CHD event rates

High Density Lipoprotein "good" cholesterol

- 20 to 30% of total serum cholesterol
- Inversely correlated with risk for CHD
- Protects against development of atherosclerosis
- Low HDL often reflects presence of other atherogenic factors
- Every 1% ↑ in HDL →1-2% ↑CHD events

# Why Do We Need Cholesterol?

Cell membrane function

- Permeability
- Fluidity
- Intracellular transport

Hormone synthesis

- Estrogen, Progesterone, Testosterone
- Cortisol, Aldosterone

Other

- Vitamin D
- Bile acids

# Lipoprotein Abnormalities: Secondary Causes

- Causes of reduced HDL

- Smoking
- Obesity
- malnutrition
- Sedentary lifestyle
- medications
  - Beta-blockers, anabolic steroids, isotretinoin, progestins

- Causes of increased HDL

- Smoking cessation
- Moderate alcohol ingestion (< 2 drinks/day)
- Physical exercise
- Weight loss
- Oral contraceptives
- Phenytoin

# Lipoprotein Abnormalities: Secondary Causes

## Hypertriglyceridemia (TG) – diet and diseases; correct when possible

- Obesity, diabetes mellitus metabolic syndrome, lipodystrophy, glycogen storage disease, ileal bypass surgery, sepsis, pregnancy
- multiple myeloma, lymphoma, acute hepatitis, systemic lupus erythematous, alcohol use/abuse

## Hypertriglyceridemia (TG) – for some drugs, the benefit outweighs the risk

- Estrogens, isotretinoin, β-blockers, glucocorticoids, **bile acid resins,** thiazides, asparaginase, interferons, azole antifungals, mirtazapine, anabolic steroids, sirolimus

# Vascular  Coronary Heart Disease

Narrowing of small blood vessels that supply oxygen to the heart due to atherosclerotic buildup

Also known as:

- Coronary artery disease
- Atherosclerosis
- Hardening/narrowing of the arteries

# Relationship of LDL to Development of CHD

## First stage

- Fatty Streak
- Most of cholesterol in fatty streaks derived from LDL

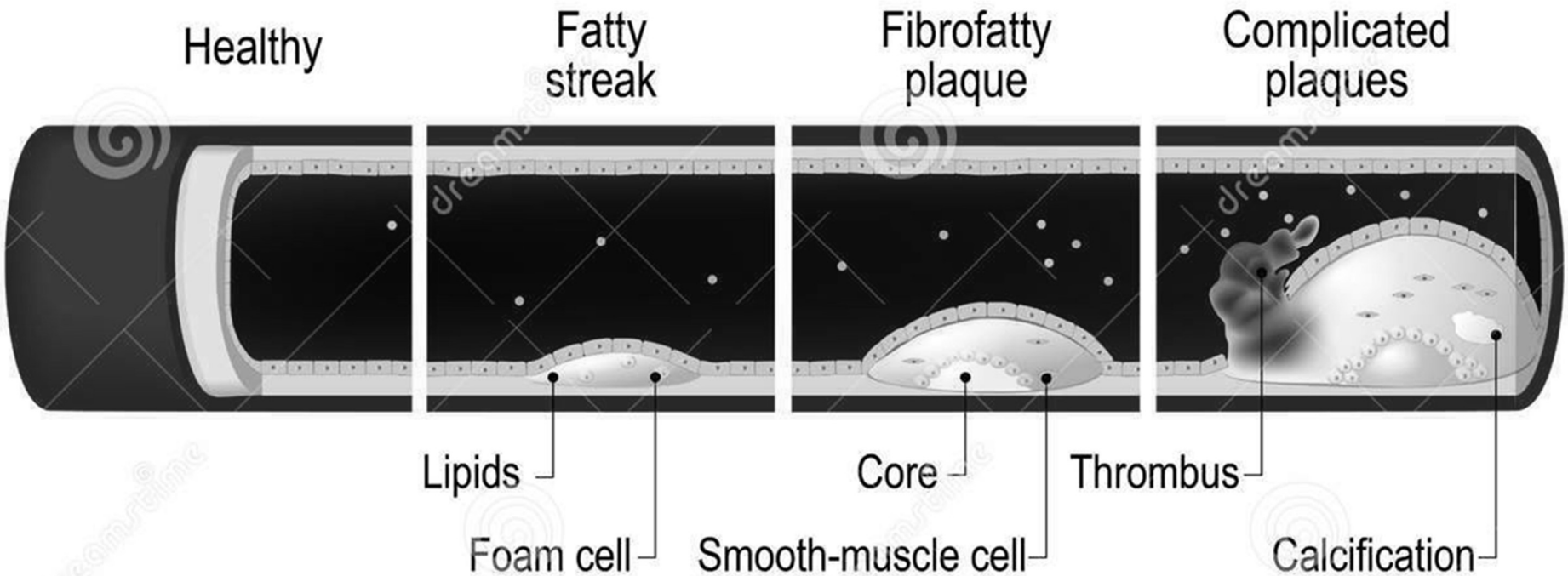
## Second Stage

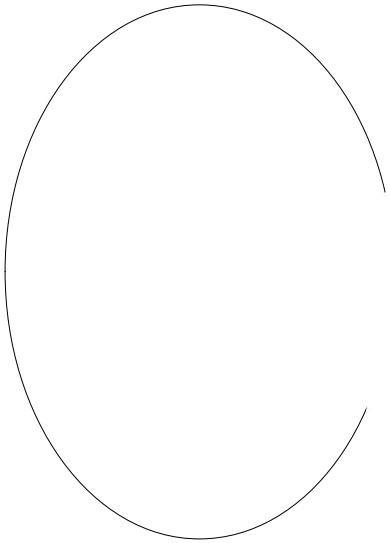
- Fibrous Plaques
- Smooth muscle cells migrate into the fatty streak, forms fibrous plaque
- Plaque begins to occlude artery
- Symptoms such as angina may start to occur

## Third Stage

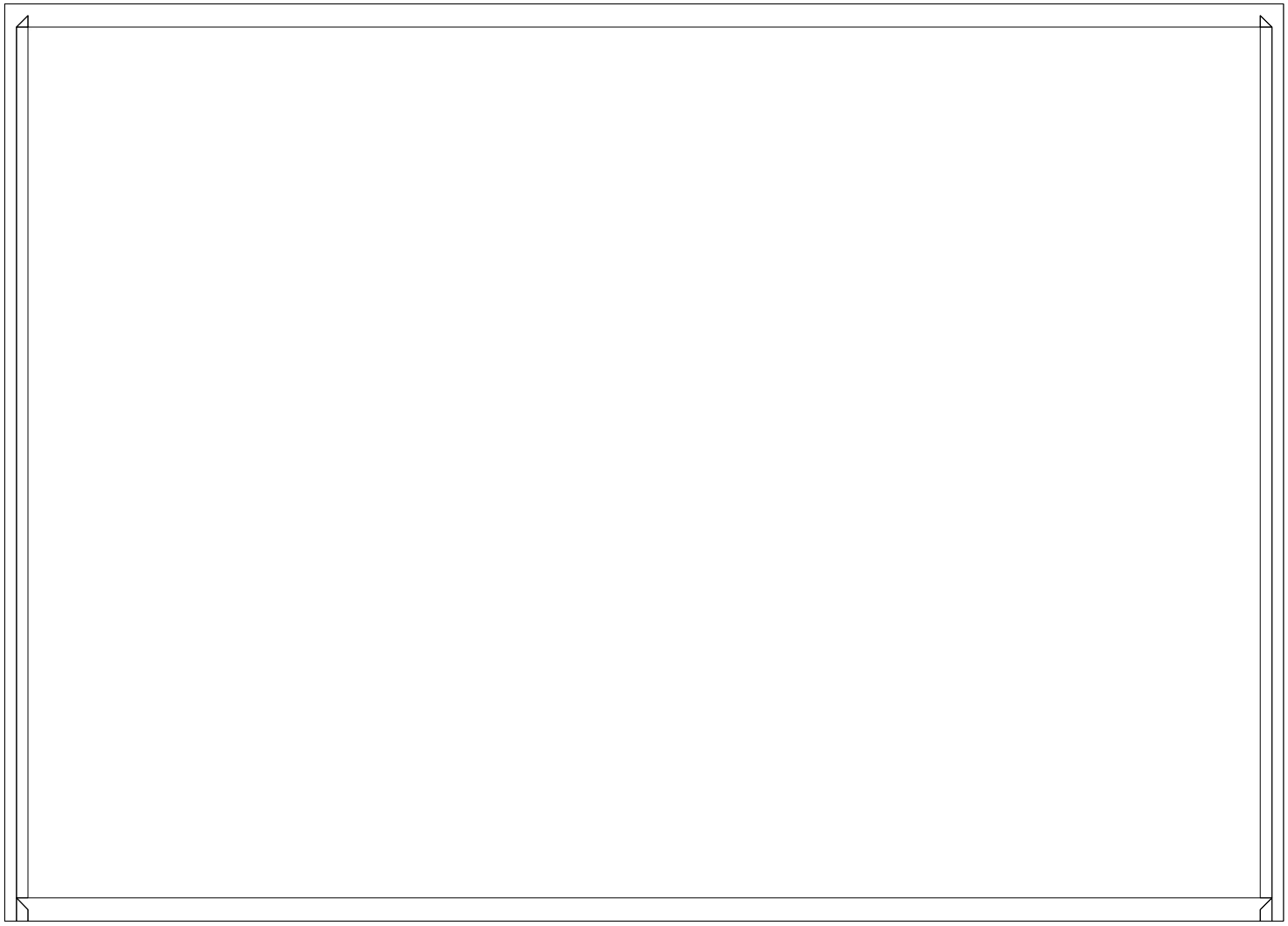
- Unstable Plaques and Thrombosis
- Prone to rupture
- Responsible for most acute coronary syndromes
- Myocardial infarction, unstable angina, coronary death

# STAGES OF ATHEROSCLEROSIS





# Relationship Between LDL, HDL, and Coronary Heart Disease



Eur Heart J 2006;8 (suppl F): F74-F80.

# Cholesterol and Cardiovascular Disease

Risk of CV disease directly related to both total cholesterol and LDL cholesterol

Increased cholesterol adds to other risk factors for coronary heart disease (CHD)

Decreased HDL is a strong independent risk factor

Triglycerides linked as a risk factor

# Dyslipidemia

- Elevation of total cholesterol
- Elevation of LDL cholesterol
- Elevation of triglycerides
- Decrease in HDL cholesterol
- Combination of the above

# Interpretation of Lipid Levels

- Lowering LDL is the primary drug therapy target.

- Triglycerides may be treated with lifestyle, and drug therapy may be considered for very high triglycerides

| **LDL Cholesterol** | |
|---|---|
| <100 | Optimal |
| 100-129 | Near optimal/above optimal |
| 130-159 | Border line high |
| 160-189 | high |
| ≥190 | Very high |
| **Total Cholesterol** | |
| <200 | Desirable |
| 200-239 | Boarder line high |
| ≥ 240 | high |
| **HDL Cholesterol** | |
| <40 | low |
| ≥ 60 | High |
| **Triglycerides** | |
| <150 | Normal |
| 150-199 | Borderline High |
| 200-499 | High |
| ≥500 | Very High |

# Clinical Presentation of High ASCVD Risk Patient

## Lab Tests:

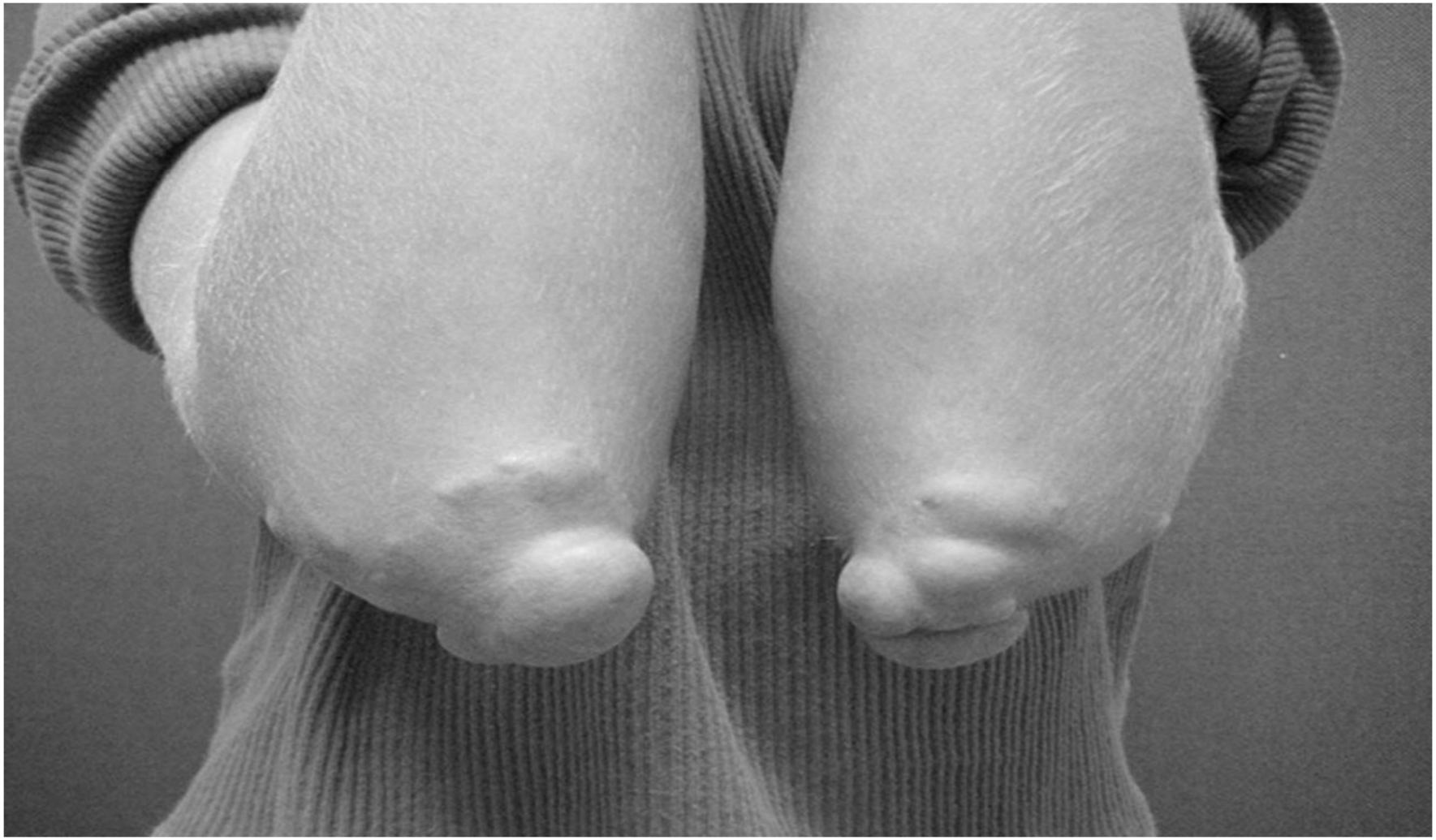
- ↑ TC
- ↑ LDL
- ↑ TG
- ↓ HDL

## Physical Assessment

- often none!
- severe abdominal pain
- pancreatitis
- eruptive xanthomas
- peripheral polyneuropathy
- HTN
- BMI > 30 kg/m2
- waist size > 40 in (men), > 35 in (women)

mednet.gr

# Cutaneous xanthomas



# Clinical Presentation

Metabolic syndrome: precursor to type 2 diabetes, increased risk of ASCVD

More than ≥ 3 of the following:

- abdominal obesity > 40 inches in men, > 35 inches in women
- TG ≥ 150 mg/dL or taking TG-lowering meds
- ↓ HDL < 40 mg/dL in men, < 50 mg/dL in women or taking lipid-lowering meds
- ↑BP ≥130/≥85 mmHg or taking BP-lowering meds
  - fasting BG ≥100 mg/dL or receiving blood glucose- lowering meds

# ACC/AHA Cholesterol Guideline

- Focus on ASCVD risk reduction
- Establishment of four statin benefit groups
- Lack of evidence to support specific LDL targets
- Evidence demonstrates that ASCVD events are reduced by using maximum tolerated statin intensity
- Creation of a new risk assessment tool for primary prevention

# ACC/AHA Risk Assessment

Begin assessing at age 20 looking for the following:

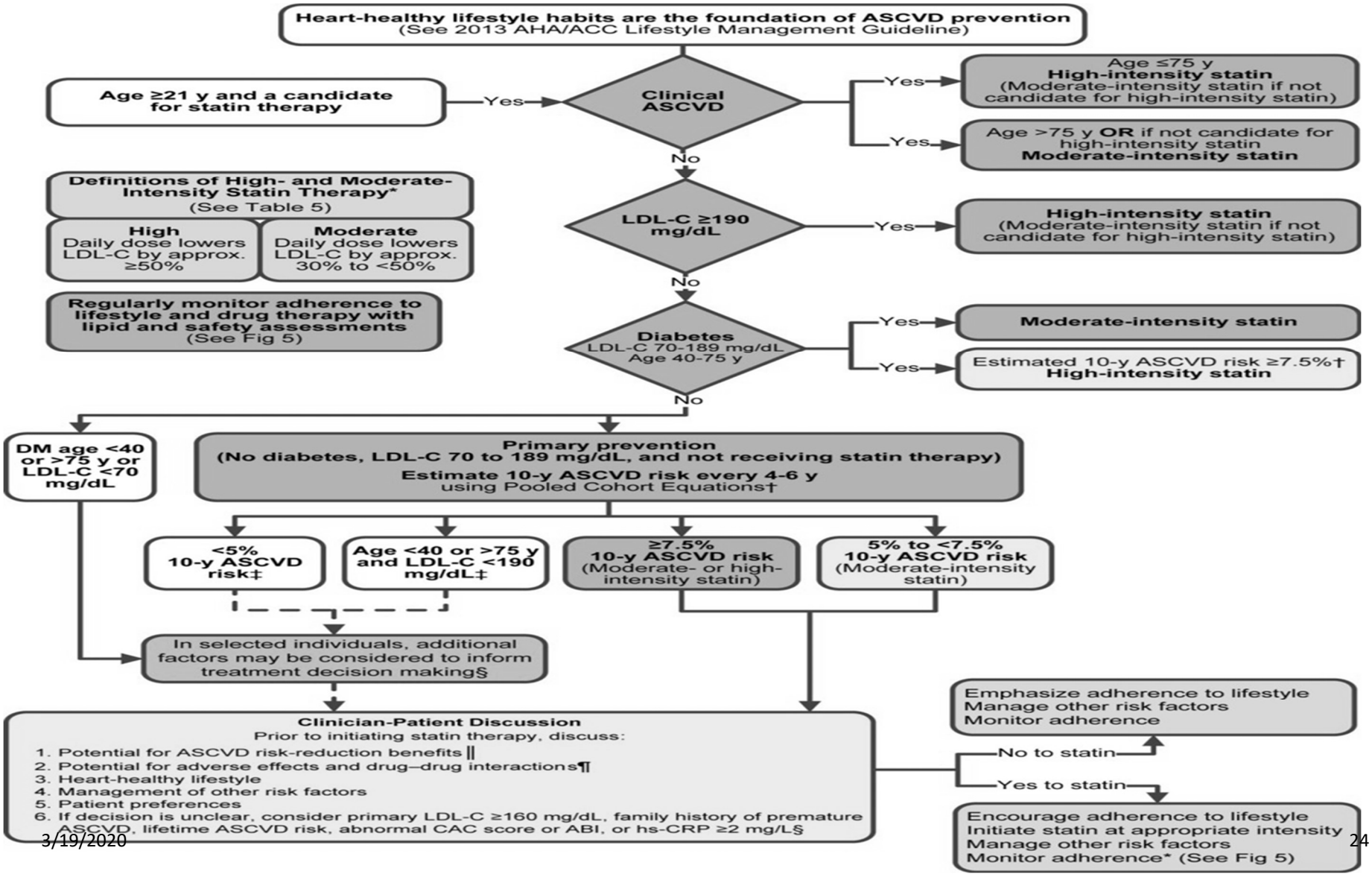
- total cholesterol and HDL-C
- systolic blood pressure
- diabetes
- smoking status

Assess every 4 to 6 years

Age 20 to 39 yo treatment options

- intensify lifestyle interventions
- DM/BP/smoking cessation drugs

# AHA/ACC Treatment Guidelines



# Steps in Managing Dyslipidemia

| | |
|---|---|
| Obtain and assess | • Obtain and assess the lipid profile |
| Determine | • Determine if patient falls into one of the four groups that benefit from statin therapy |
| Determine | • Determine intensity of statin therapy |
| Initiate | • Initiate statin therapy |
| Counsel on | • Counsel on healthy lifestyle |
| Monitor and adjust | • Monitor and adjust therapy |



2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: J Am Coll Cardiol 2013

# Step 1 – Obtain Lipid Profile

Lipid profile should be fasting

Total cholesterol = LDL + HDL + VLDL

VLDL = Triglyceride/5

LDL is usually a calculated value

LDL = TC – HDL – (TG/5)

- Friedewald equation*: LDL = TC – HDL – (TG/5)

*Can be used when TG <400mg/dL

# Step 2 – Determine If Patient Benefits from Statin Therapy

**<u>Four groups that benefit from statin therapy</u>**:

1) Clinical ASCVD ≥ 21 yo Clinical atherosclerotic cardiovascular disease (ASCVD) - includes CHD, stroke, TIA, and peripheral arterial disease

2) LDL cholesterol ≥ 190 mg/dL

3) Type 1 or 2 diabetes (ages 40-75 years)

LDL-C 70 – 189 mg/dL

4) No ASCVD or Diabetes LDL-C 70 – 189 mg/dL 10 yr risk ≥ 7.5%



2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: J Am Coll Cardiol 2013..

# Cardiovascular Risk Calculator

Provides 10-year risk estimate for patients ages 40-79

Provides lifetime risk estimate for patients ages 20-59

Risk of 7.5% is the threshold for therapy decisions

Step 3 Determine Intensity of statin therapy

## High-intensity

- Clinical ASCVD and age ≤ 75
- LDL cholesterol ≥ 190 mg/dL
- Diabetes (ages 40-75) with 10-year risk of ASCVD ≥ 7.5%

## Moderate-intensity

- Clinical ASCVD and age > 75
- Diabetes (ages 40-75) with 10-year risk < 7.5%
- Patients who cannot tolerate high-intensity

# Step 3 Determine intensity of statin Therapy

## Moderate- or high-intensity

St

- Others (ages 40-75) with LDL 70 – 189 mg/dL and 10- year risk of ASCVD ≥ 7.5%

statin Therapy

## Consider moderate-intensity

- Others (ages 40-75) with LDL 70 – 189 mg/dL and 10- year risk of ASCVD 5% - < 7.5%

## Not generally recommended

- Patients with 10-year risk of ASCVD < 5%

## Individualize treatment decisions

## Consider patient preferences and other factors

# Step 4 – Initiate Statin Therapy

## High-intensity therapy

- Lowers LDL cholesterol by ≥ 50%
- Atorvastatin 80 mg (40 mg)
- Rosuvastatin 20 or 40 mg

## Moderate-intensity therapy

- Lowers LDL cholesterol by 30 to < 50%
- Lower doses of atorvastatin
- Lower doses of rosuvastatin
- Higher doses of other statins

# Statin Potency

**Table 1. High-Intensity and Moderate-Intensity Statin Therapy, According to 2013 American College of Cardiology–American Heart Association (ACC-AHA) Cholesterol Guidelines.**

**High-intensity statin therapy**

Daily dose lowers LDL cholesterol level by approximately ≥50% on average

Recommended: atorvastatin, 40 to 80 mg; rosuvastatin, 20 to 40 mg

**Moderate-intensity statin therapy**

Daily dose lowers LDL cholesterol level by approximately 30 to <50% on average

Recommended: atorvastatin, 10 to 20 mg; rosuvastatin, 5 to 10 mg; simvastatin, 20 to 40 mg; pravastatin, 40 to 80 mg; lovastatin, 40 mg; extended-release fluvastatin, 80 mg; fluvastatin, 40 mg twice a day; pitavastatin, 2 to 4 mg

# Statins

Inhibit HMG-CoA conversion to mevalonate

- Primarily reduce LDL
- May also ↓ TG and ↑HDL

Reduce CHD morbidity and mortality

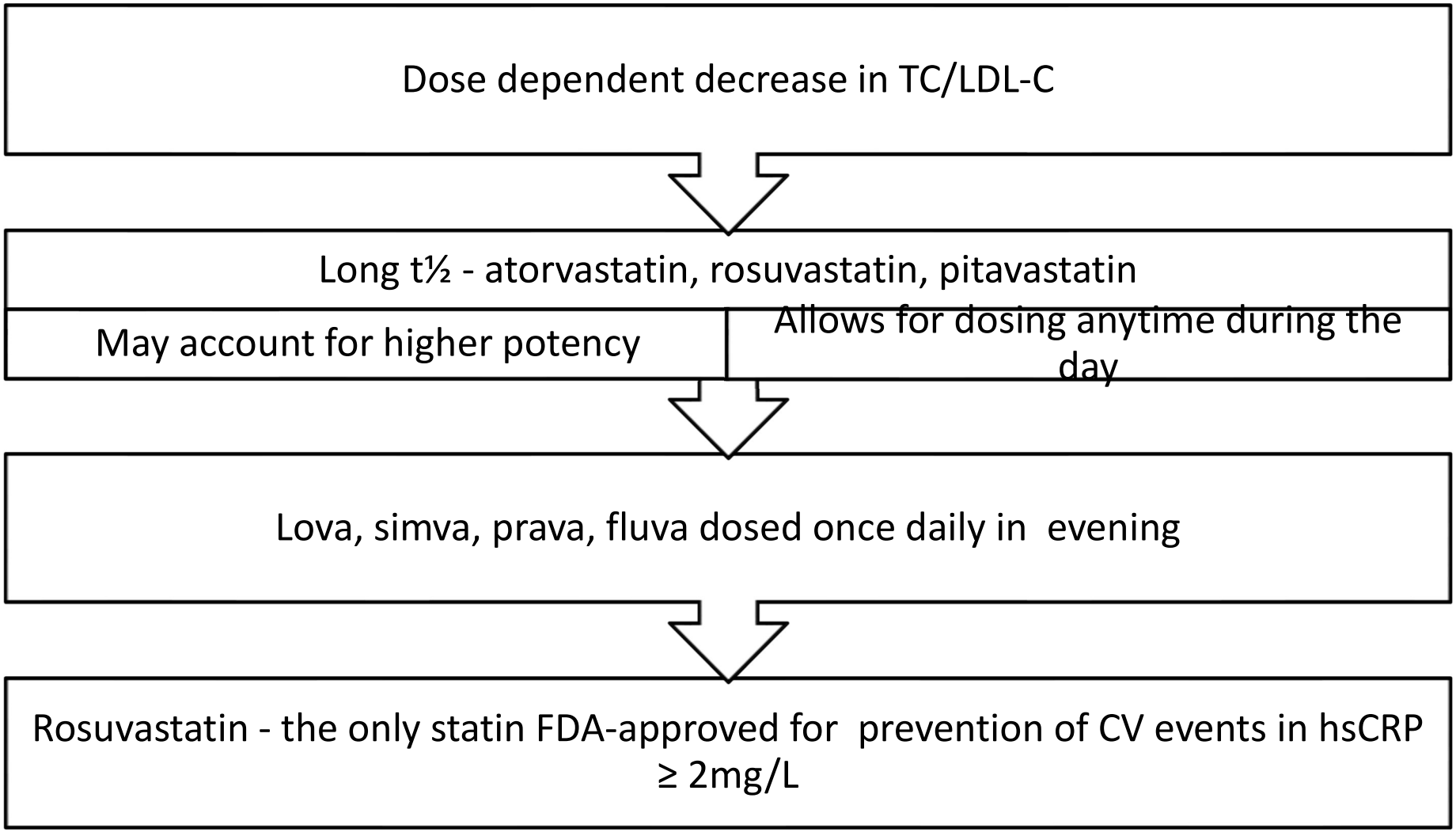
First-line therapy for LDL-lowering

Administered once daily – usually HS

Dose dependent decrease in TC/LDL-C

Contraindications – pregnancy, breastfeeding, active liver disease

# HMG-CoA Reductase Inhibitors



# Statin Pharmacokinetics



| Statin | Half-Life (h) | Lipophilic | Metabolism |
|---|---|---|---|
| Fluvastatin | 1.2 | Y | 2C9 |
| Pravastatin | 1.8 | N | None |
| Lovastatin | 3 | Y | 3A4* |
| Pitavastatin | **12** | Y | UGT1A3/UGT2B7 |
| Simvastatin | 2 | Y | 3A4* |
| Atorvastatin | **7-14** | Y | 3A4* |
| Rosuvastatin | **13-20** | N | 2C9/2C19* |

# LDL-Lowering of Various Statins

5

| Generic | Brand | Dosage range | LDL reduction |
|---|---|---|---|
| Fluvastatin | Lescol® | 20 – 80 mg | 22 - 36% |
| Pravastatin | Pravachol® | 10 – 80 mg | 22 - 37% |
| Lovastatin | Mevacor® | 10 – 80 mg | 21 - 42% |
| Pitavastatin | Livalo® | 1 – 4 mg | 32 - 43% |
| Simvastatin | Zocor® | 5 – **80 mg** | 25 - 47% |
| Atorvastatin | Lipitor® | 10 – 80 mg | 39 - 60% |
| Rosuvastatin | Crestor® | 5 – 40 mg | 45 - 63% |

# Statins and Muscle Safety

Muscle symptoms are most common adverse effect

Myalgias : muscle ache or weakness w/o CK elevation

Myopathy any disease of the muscle

- Symptoms + creatine kinase (CK)
- 5 per 100,000 person-years

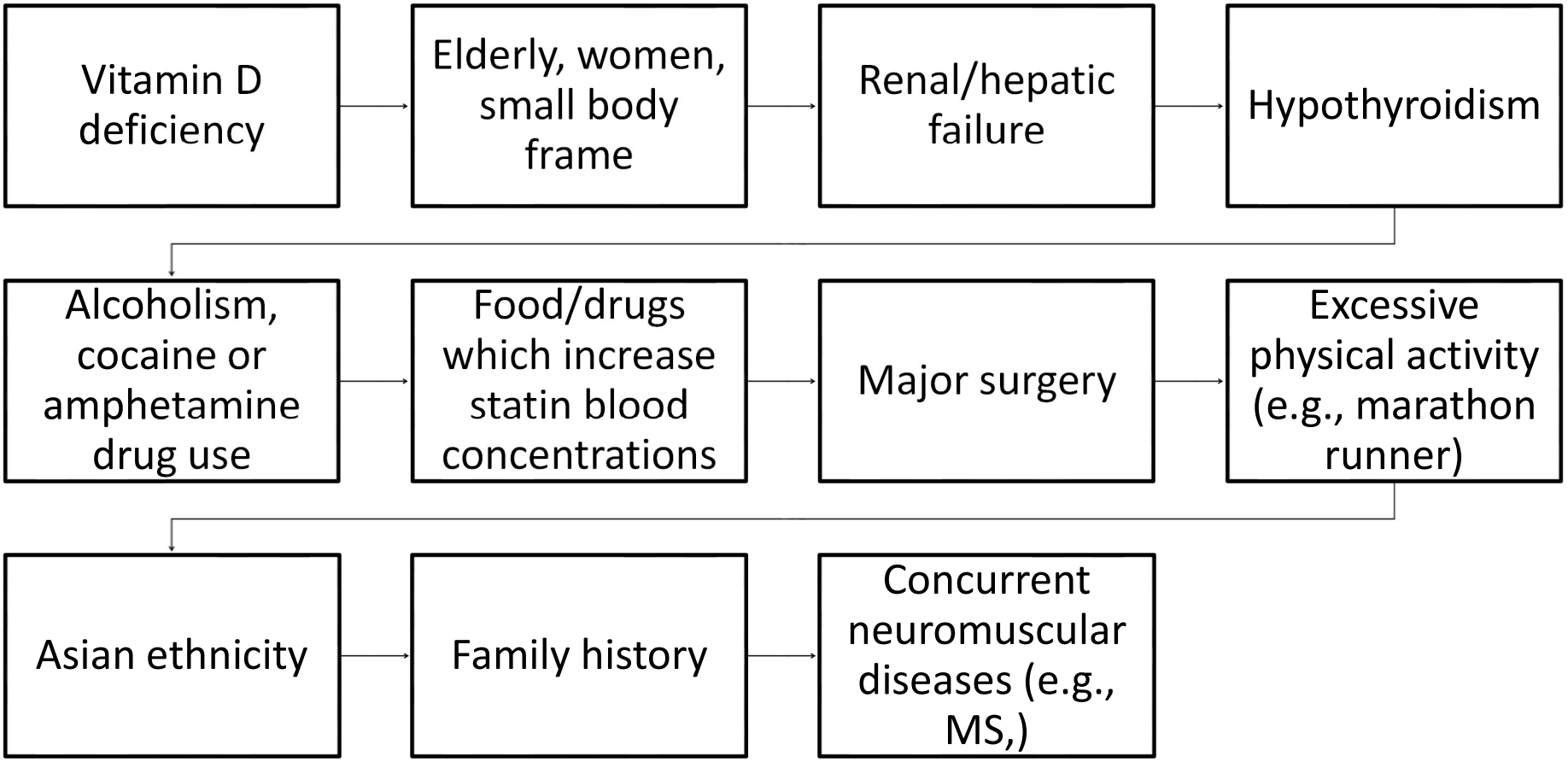
Rhabdomyolysis: muscle ache or weakness w/significant CK elevation

Baseline CK not required

Routine CK monitoring not required in asymptomatic

Check CK in those with symptoms

# Myalgia Risk Factors



# Myalgia Preventive Management

- Start with a low intensity statin dose
- Vitamin D supplementation if low
- Less lipophilic statin such as pravastatin or rosuvastatin
- Intermittent dosing +/- non-statin adjunctive therapy
- Holding statin in high-risk patients when undergoing major surgery

# Myalgia Management

## Mild to Moderate Myalgia Management

- Stop statin and evaluate for risk factors
- If no contraindication & myalgia resolves, consider rechallenge with the same statin at same or lower dose
- If myalgia or elevated CK does not resolve in 2 months, evaluate further for muscle disease
- If rechallenge results in myalgia again, consider alternative statin at low intensity & increase dose as tolerated
- If muscle pain is being treated and not secondary to statins, can consider statin rechallenge – consider alternate day therapy

## Severe Myalgia Management

- Stop statin
- Check CK, serum creatinine, myoglobinuria
- Consider once weekly or other alternate non-statin therapy

# Drug Interactions with Simvastatin

Grapefruit juice

## Never Use With

- Azole antifungals (ketoconazole, voriconazole, posaconazole)
- Macrolide antibiotics (erythromycin, clarithro, telithro)
- Nefazodone
- HIV & Hep C protease inhibitors – indinavir, ritonavir, atazanavir, darunavir, saquinavir, tipranavir, loprinavir, boceprevir, telaprevir, nelfinavir, amprenavir, fosamprenavir
- Danazol

## Avoid use with

- Cyclosporine, tacrolimus, sirolimus, everolimus
- Gemfibrozil

## Limit to 10 mg

- Diltiazem
- Verapamil

## Limit to 20 mg

- Amiodarone
- Amlodipine
- Ranolazine

# Simvastatin & FDA Recommendations

FDA recommends that healthcare professionals should:

- Maintain patients on simvastatin 80 mg only if they have been taking this dose for 12 or more months without evidence of muscle toxicity.
- Not start new patients on simvastatin 80 mg.
- Place patients who do not meet their LDL cholesterol (LDL-C) goal on simvastatin 40 mg on alternative LDL-C lowering treatment(s) that provides greater LDL-C lowering (see Relative LDL-lowering Efficacy of Statin and Statin-based Therapies below).
- Follow the recommendations in the simvastatin-containing medicines labels regarding drugs that may increase the risk for muscle injury when used with simvastatin (see Simvastatin Dose Limitations below).
- Switch patients who need to be initiated on a drug that interacts with simvastatin to an alternativ statin with less potential for the drug-drug interaction.
- Report adverse events involving simvastatin-containing medicines to the FDA MedWatch program using the information in the "Contact Us" box at the bottom of this page.

# Atorvastatin

## Never use with

- HIV & Hep C protease inhibitors such as ritonavir, atazanavir, darunavir, boceprevir, telaprevir
- Posaconazole

## Avoid use with

- Ketoconazole, voriconazole, Gemfibrozil, Verapamil, Rivaroxiban, Gemfibrozil
- Cyclosporine

## Monitor ADEs with

- Macrolide antibiotics (erythromycin, clarithro, telithro)
- Diltiazem
- Amiodarone, dronaderone

# Lovastatin

## Never use with

- Azole antifungals (ketoconazole, posaconazole, voriconazole)
- Macrolide antibiotics (erythromycin, clarithro, telithro
- HIV & Hep C protease inhibitors – indinavir, ritonavir, atazanavir, darunavir, saquinavir, tipranavir, loprinavir, boceprevir, telaprevir, nelfinavir, amprenavir, fosamprenavir
- Conivaptan, Nefazodone, Cobicistat, Idelalisib

## Avoid use with

- Cyclosporine, tacrolimus, sirolimus, everolimus, Gemfibrozil

## ≤ 20mg

- Danazol, Diltiazem, verapamil, Dronedarone

## ≤ 40mg

- Amiodarone
- Ticagrelor

# Statins and Liver Safety

## AST or ALT > 3 X ULN

- <1% of patients on starting/intermediate doses
- 2-3% of patients on 80mg of statin

## Monitor LFTs

- Before initiation of therapy
- As clinically indicated thereafter

## AST or ALT 1-3 X ULN

- Repeat testing
- Continue

## AST or ALT > 3 X ULN

- Repeat testing
- Continue, decrease or discontinue

# Other Statin Safety Issues

Category X in pregnancy

Hemorrhagic stroke/risk of bleeding

consider low to mod intensity

Decrease dose if LDL-C < 40 mg/dL

- Bleeding risk or male infertility

Cognitive impairment

Relatively uncommon

- Memory loss or impairment
- Reversible upon discontinuation

# Other Statin Recommendations

Simvastatin 80mg daily

only in patients who have been taking for ≥ 12 months

Simva, lova or atorva + warfarin

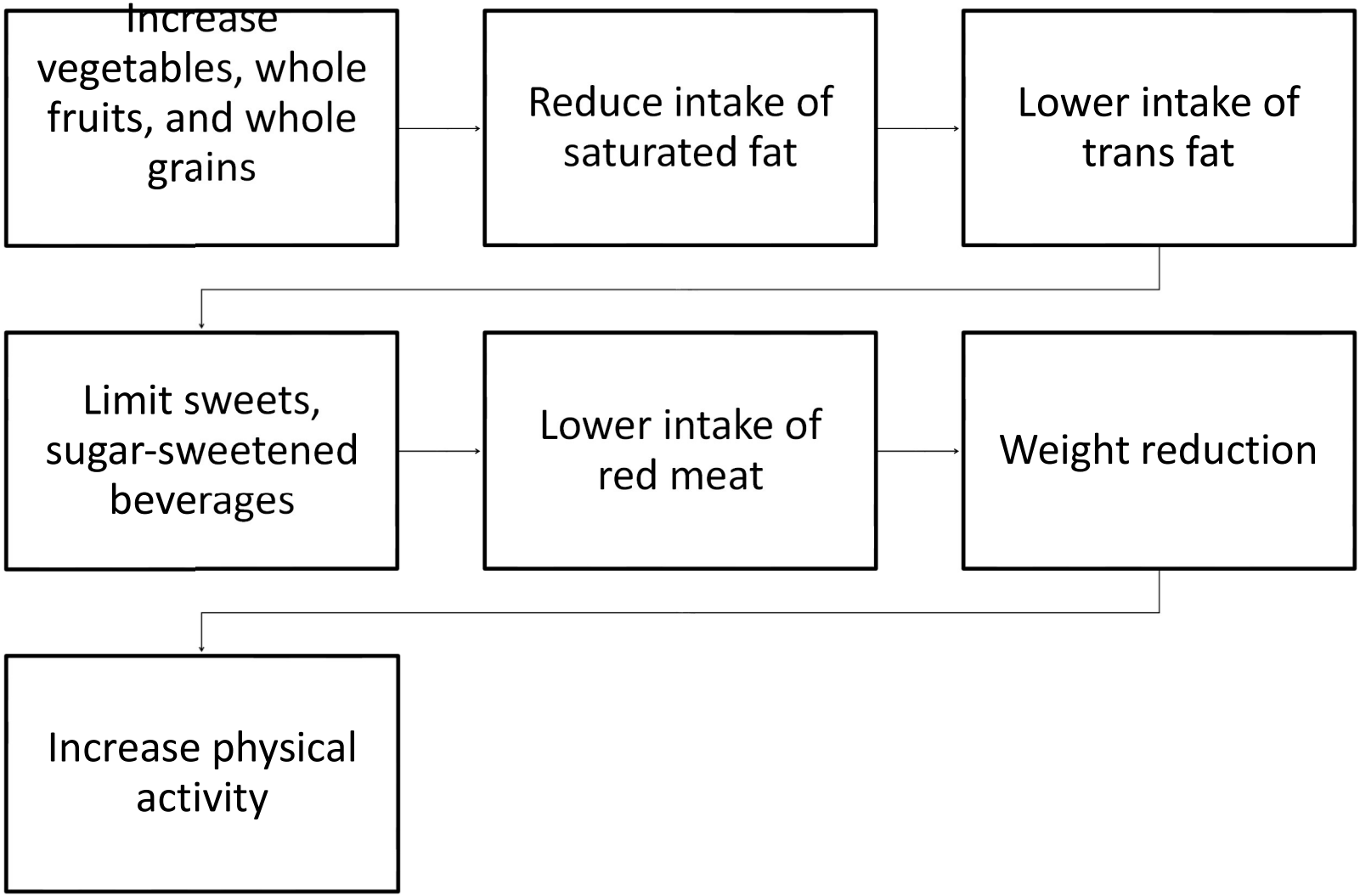
↑INR, bleeding

Simva, lova or atorva + grapefruit

↑ myalgia risk

Consider non-statin adjunctive therapy with lower or intermittent statin dosing if unable to tolerate

# Step 5 – Counsel on Healthy Lifestyle



# Healthy Lifestyle Changes

Reduce intake of saturated fat

5-6% of calories from saturated fat

Raises LDL cholesterol more than any other dietary component

Solid at room and refrigerator temperature

Fat from animal sources

- Fatty meats
- Poultry skin
- Whole-milk dairy products

# Healthy Lifestyle Changes

## Reduce intake of trans fat

- Hydrogenated vegetable oils (margarine)

## Unsaturated fats (monounsaturated, polyunsaturated)

- Help to lower cholesterol
- Liquid at room temperature
- Olive, canola, sunflower, peanut
- Nuts
- Avocados
- Omega-3 fatty acids

il

# Healthy Lifestyle Changes

## Achieve and maintain healthy weight

- Body mass index
- Waist circumference
  - > 40 inches in men
  - > 35 inches in women

## Increase physical activity

- 3 to 4 times per week
- 40 minutes per session
- Moderate-vigorous level

# Obesity Guidelines

Overweight (BMI >25.0-29.9 kg/m2)

Obese (BMI ≥30 kg/m2)

Sustained weight loss of 3%-5% produces health benefits

- 1,200–1,500 kcal/day for women and 1,500–1,800 kcal/day for men
- 500 kcal/day or 750 kcal/day energy deficit

Bariatric surgery

- BMI ≥40
- BMI ≥35 with comorbid conditions, with motivation and who have not responded to treatment

# Step 6 – Monitor/Adjust Therapy

Initiate statin therapy

Follow-up in 4-12 weeks – fasting lipid profile

Anticipated response

- High-intensity – LDL ¯ ≥ 50% from untreated baseline
- Moderate-intensity - LDL ¯ by 30 - < 50% from baseline
- Monitor every 3-12 months as needed

Less than anticipated response

- Inquire about adherence or adverse effects
- Intolerance - switch statin or modify intensity
- Increase intensity??
- Follow-up in 4-12 weeks

# Other Cholesterol-Lowering Agents

- Bile acid sequestrants
- Cholesterol absorption inhibitor
- PCSK9 inhibitors
- Fibric acid derivatives
- Niacin
- Fish oil

# Bile Acid Sequestrants

Bind to intestinal bile acids to form insoluble complex that is eliminated

- increase fecal bile excretion → ↑ LDL-C excretion
- stimulate bile acid synthesis from cholesterol
- upregulate LDL receptors →↑ LDL-C breakdown
- **Mainly Decrease LDL↓15-30%**

May increase TG

- caution if TG ≥ 250 to 299 mg/dL
- contraindicated if TG > 300 mg/dL
- Discontinue if TG > 400 mg/dL

# Bile Acid Sequestrants

Colesevelam Pregnancy category B and not excreted in breast milk, not systemically absorbed

Agents

- Cholestyramine (Questran®)
- Colestipol (Colestid®)
- Colesevelam (Welchol®)

# Bile Acid Sequestrants

## Dosing (normal ranges)

- Cholestyramine (4 g packets): 4 – 16 g/day
- Colestipol (5 g packets): 5 – 20 g/day; (1 g tabs): 2-16 g/day
- Colesevelam (625 mg tabs): 6 tabs daily; (3.75 g packet): daily

## Adverse effects

- GI discomfort, constipation – frequently used for diarrhea mgmt
- titrate slowly, increase fluid intake, increase dietary bulk, add stool softeners or stimulant laxatives

# Bile Acid Sequestrants

## Concerns

- Drug interactions (separate by 4 hours)
- Take other medications at least 1 to 2 hours before or 4 to 6 hours after taking BAS
- ↓absorption of medications (ex: warfarin, niacin, digoxin, levothyroxine, etc)
- impair fat soluble vitamin absorption – separate dosing
- A, D, E, K
- Tablet burden or intolerance to powder

## Place in therapy

- May be considered as add-on to statin therapy
- In patients unable to tolerate statins
- Colesevelam (Welchol®) preferred QD dosing, 6 or fewer tabs/day

# Cholesterol Absorption Inhibitor

- Inhibits absorption of cholesterol in the small intestine:
- Agent: Ezetimibe (Zetia®)
- Lowers LDL ~ 18%
- May be combined with statin
- Well tolerated dosed once daily without regard to meals
- Caution with fibrates (use fenofibrate)
- Combination product – ezetimibe/simvastatin (Vytorin®)

# PCSK9 Inhibitors

Monoclonal antibody

Inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9) binding to LDL receptors to promote LDL receptor degradation

# PCSK9 Inhibitors

## Agents

- Alirocumab (Praluent®)
- Evolocumab (Repatha™)

## Indications

- Adjunct to other therapies in familial homozygous hypercholesterolemia*
- Adjunct to statins in heterozygous familial hypercholesterolemia or patients with ASCVD who need additional LDL lowering

## Substantial LDL-C lowering

- Monitor LDL-C in 4-8 weeks
- Evolocumab: ≥ 36% to 76%
- Alirocumab: ≥ 30% to 67%

## Administration

- Subcutaneous injection every 2 weeks (or monthly*)

## Cost - ~ $14,000 prer yea

# Alirocumab

Praluent®

- Store in refrigerator and warm to room temp 30-40 min
- Stable for 24 hours at room temperature; do not shake

SC in abdomen, thigh, or upper arm

No dosage adjustments for mild to moderate renal or hepatic impairment; no information on use in severe renal/hepatic disease

# Evolocumab

Repatha®

- store in refrigerator, warm to room temp 30 -45 min
- room temp stable for 30 days

HeFH: SC every 2 weeks or once monthly in abdomen, thigh, or upper arm

HoFH: SC once monthly over 9 minutes by using the single-use on-body infusor with prefilled cartridge, or by giving 3 injections consecutively within 30 minutes using the single-use prefilled autoinjector or single-use prefilled syringe.

No dosage adjustments for mild to moderate renal or hepatic impairment; no information on use in severe renal/hepatic disease

# Hypertriglyceridemia

Increased ASCVD risk due to insulin resistance and metabolic syndrome

Elevated non-HDL-C = ↑ ASCVD risk

Statin therapy may be added in the face of elevated LDL-C to lower ASCVD risk

Evaluate for secondary causes of high TGs

Optimal TG < 100 mg/dL, Lifestyle modifications, Reduce ETOH

# Hypertriglyceridemia

Treat if > 500 mg/dL

Diet and exercise if ≤ 500 mg/dL

- 5 to 10% weight loss = ↓ 20%
- Mediterranean diet = ↓ 10 to 15%
- fish based omega-3 fatty acids = ↓5 to 10%
- moderately intensive exercise 150 min/week
- smoking cessation
- alcohol restriction
- decrease carbohydrates, saturated/trans fat

| Nutrition Practice | TG-Lowering Respon |
|---|---|
| Weight loss (5% to 10% of body weight) | 20 |
| Implement a Mediterranean-style diet vs a low-fat diet | 10–15 |
| Add marine-derived PUFA (EPA/DHA) (per gram) | 5–10 |
| Decrease carbohydrates | |
| 1% Energy replacement with MUFA/PUFA | 1–2 |
| Eliminate *trans* fats | |
| 1% Energy replacement with MUFA/PUFA | 1 |

TG indicates triglyceride; PUFA, polyunsaturated fatty acid; EPA, eicosa taenoic acid; DHA, docosahexaenoic acid; and MUFA, monounsaturated acid.

# Management of Elevated TG

# Hypertriglyceridemia

| DRUG | TG Lowering |
|---|---|
| Fibrates | 30 to 50% |
| Immediate release niacin | 20 to 50% |
| Omega-3 FA | 20 to 50% |
| Extended release niacin | 10 to 30% |
| Statins | 10 to 30% |
| Ezetimibe | 5 to 10% |

- If TG > 500 mg/dL, evaluate for secondary causes
- Risk of pancreatitis
- Drug therapy is reasonable if TG > 500 mg/dL

# Fibric Acid Derivatives (Fibrates)

## MOA

- Increase synthesis of lipoprotein lipase →increase clearance of VLDL-C
- Mainly decrease TG; also increase HDL and lower LDL (variable)

## Agents

- Gemfibrozil (Lopid®) – dose 30 minutes before meals BID
- Fenofibrate (Tricor®, Triglide®) – dose without regard

## Adverse effects –

- GI, gall stones, myalgias

## Caution in renal insufficiency

- avoid severe renal disease (CrCl < 30 mL/min)

## Metabolized by liver

- - ↑ ALT/AST & alkaline phosphatase
- Avoid severe liver disease (LFTs ≥ 3x ULN)

# Fibric Acid Derivatives (Fibrates)

Caution with statins - rhabdomyolysis (gemfibrozil)

Gemfibrozil – contraindicated with simvastatin and repaglinide; avoid with statins if possible

Potentiate effects of oral Vit K antagonists (gemfibrozil> fenofibrate)– monitor PT/INR closely

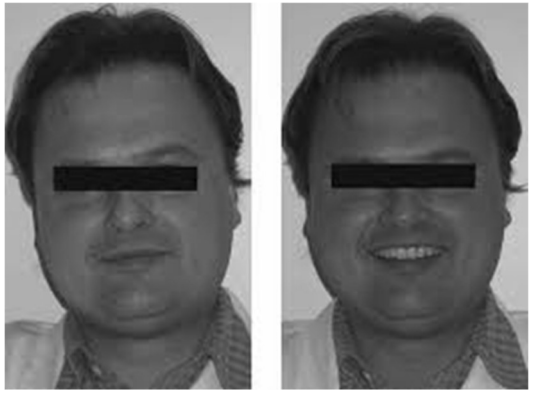
Gemfibrozil safe for use during and after 2nd trimester

Myalgia or myopathy risk

# Statin-Fibrate Combination

NLA Task Force on Statin Safety - 2014 update. Journal of Clinical Lipidology 2014;8:S1-S81.

# Nicotinic Acid/Niacin



OTC and prescription, vitamin B3

Second line after fibrates to lower TGs

Increased myopathy risk when combined with statins, fibrates

AIM HIGH trial did not show clinical benefit against simvastatin

Worsening blood sugars, PUD, hyperuricemia and hepatoxicity

Cutaneous flushing →

- aspirin 81mg to 325mg 30 minutes prior to dosing
- Slow titration due to GI symptoms
- A common starting dose for immediate-release niacin is 100 mg two to three times a day or 250 mg two times a day after meals.

Laboratory abnormalities

- Elevated LFTs, Increased glucose, Increased uric acid

# Administration of Niacin

http://www.niaspan.com/information_on_flushing.pdf

# Fish Oil

## Omega-3 fatty acids – EPA and DHA

## Mainly used for TG reduction

## Availability

- OTC (look for EPA and DHA)
- Rx EPA with DHA (Lovaza®) – for TG ≥ 500
- Rx Icosapent ethyl – EPA (Vascepa®) – for TG ≥ 500

## Adverse effects

- Belching
- Indigestion
- Fishy taste

# Omega 3 Fatty Acids

< 3 g/day generally recognized as safe

2 to 4 g of EPA & DHA may be used for very high TG

Availability

- OTC (look for EPA and DHA)
- Rx EPA with DHA (Lovaza®) – for TG ≥ 500
- Rx Icosapent ethyl – EPA (Vascepa®) – for TG ≥ 500
- Eleven capsules a day will equal the dose of the prescription product
- Take with meals to improve tolerability

Adverse effects:

- GI disturbance, fishy aftertaste, belching
- increased bleeding risk, thrombocytopenia
- worsening glycemic control
- increased LDL-C
- abnormal LFTs

# Summary of Lipid Lowering Agents and Effects on the Lipid Profile



| Agent | LDL-C | HDL-C | TG |
|---|---|---|---|
| Statins | ↓18-63% | ↑5-15% | ↓7-30% |
| Bile acid sequestrants | ↓15-30% | ↑3-5% | No Δ or ↑ |
| Ezetimibe | ↓18-20% | ↑1-4% | ↓8% |
| Fibric acid derivatives | ↓5-20% | ↑10-20% | ↓20-50% |
| Niacin | ↓5-25% | ↑15-35% | ↓20-50% |
| Fish oil | No Δ or ↑ | ↑3-10% | ↓14-45% |

# Monitoring

| | |
|---|---|
| Statins<br>(adherence) | Baseline FLP (NF LP acceptable if non-HDL-C < 220), LFTs, possibly CK if pt is higher risk<br>Repeat LFTs periodically and if hepatic symptoms occur<br>Repeat FLP at 4 to 12 weeks and every 3 to 12 months thereafter<br>CK if muscle symptoms occur |
| Bile Acid Resins | Baseline FLP, LFTs<br>Repeat FLP at 3 months and every 6 to 12 months thereafter<br>If TG 250-299, FLP at 4 to 6 weeks |
| Nicotinic Acid | Baseline FLP, fasting glucose, LFTs, uric acid<br>Repeat all tests during dose change and every 6 months thereafter |
| Fibric Acid | Baseline FLP, LFTs, serum creatinine<br>Repeat FLP at 6 wks and at 6 to 12 months, periodically thereafter<br>Repeat serum creatinine at 3 months & every 6 months thereafter |
| Cholesterol Absorption Inhibitors | Baseline FLP, LFTs<br>Repeat LFTs periodically thereafter if administered with statin |
| Omega-3 Fatty Acids | Baseline FLP, fasting glucose and periodically thereafter |

# Summary of Dyslipidemia

- Hyperlipidemia increases the risk of CHD
- Statins lower LDL and the risk of CHD events
- 4 groups of patients benefit from statin therapy
- Moderate- or high-intensity therapy is recommended
- Other drugs for LDL – bile acid sequestrants, ezetimibe, PCSK9 inhibitors
- Drugs for TG – fibrates, niacin, fish oil
- For HDL – lifestyle