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

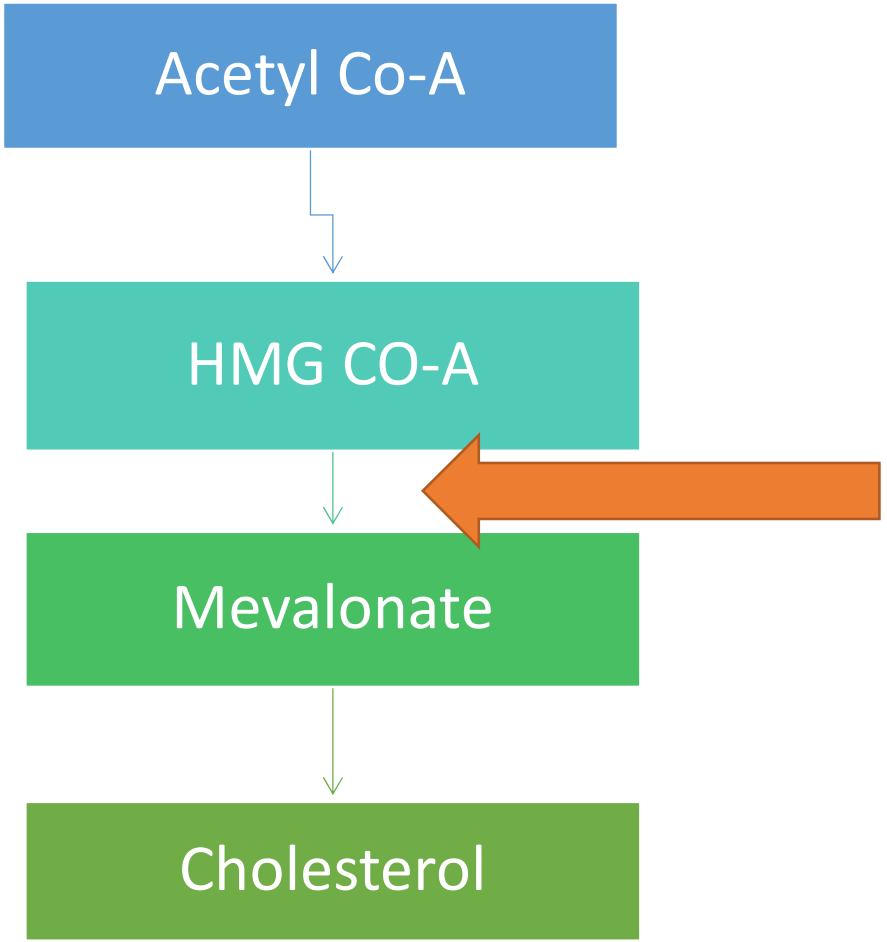
- < 180mg/dL = 15% risk of death

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



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

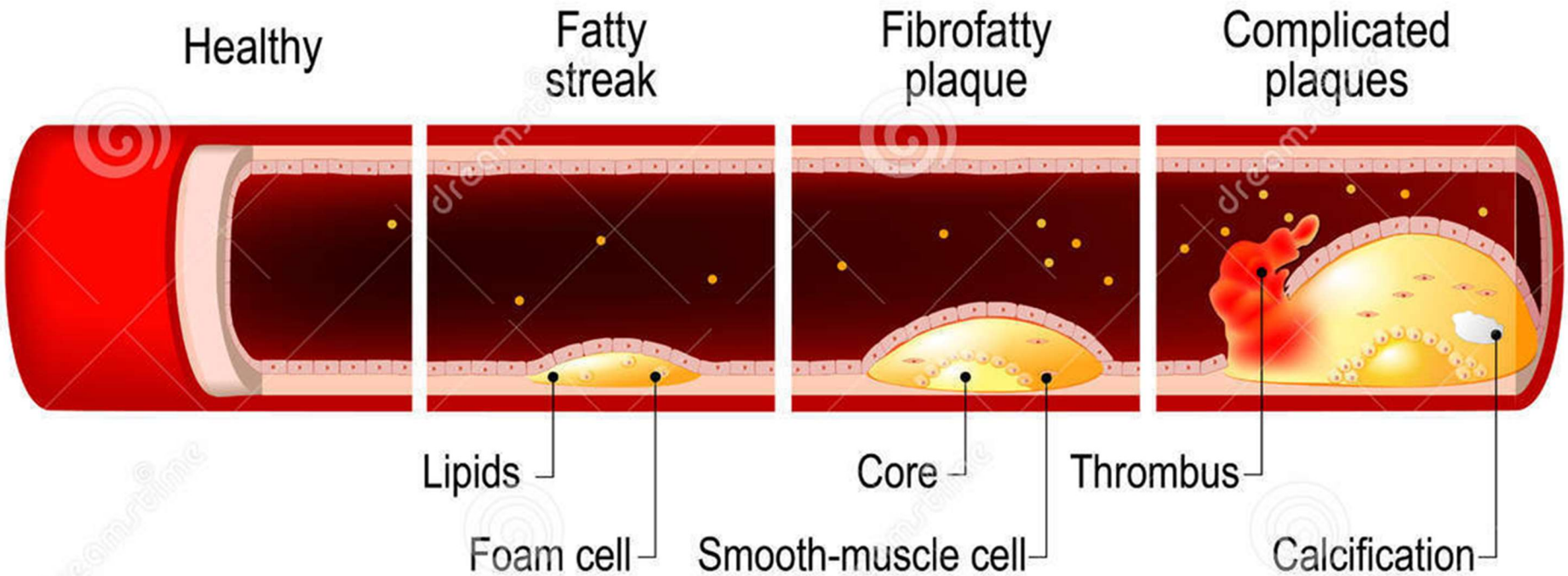
Second Stage

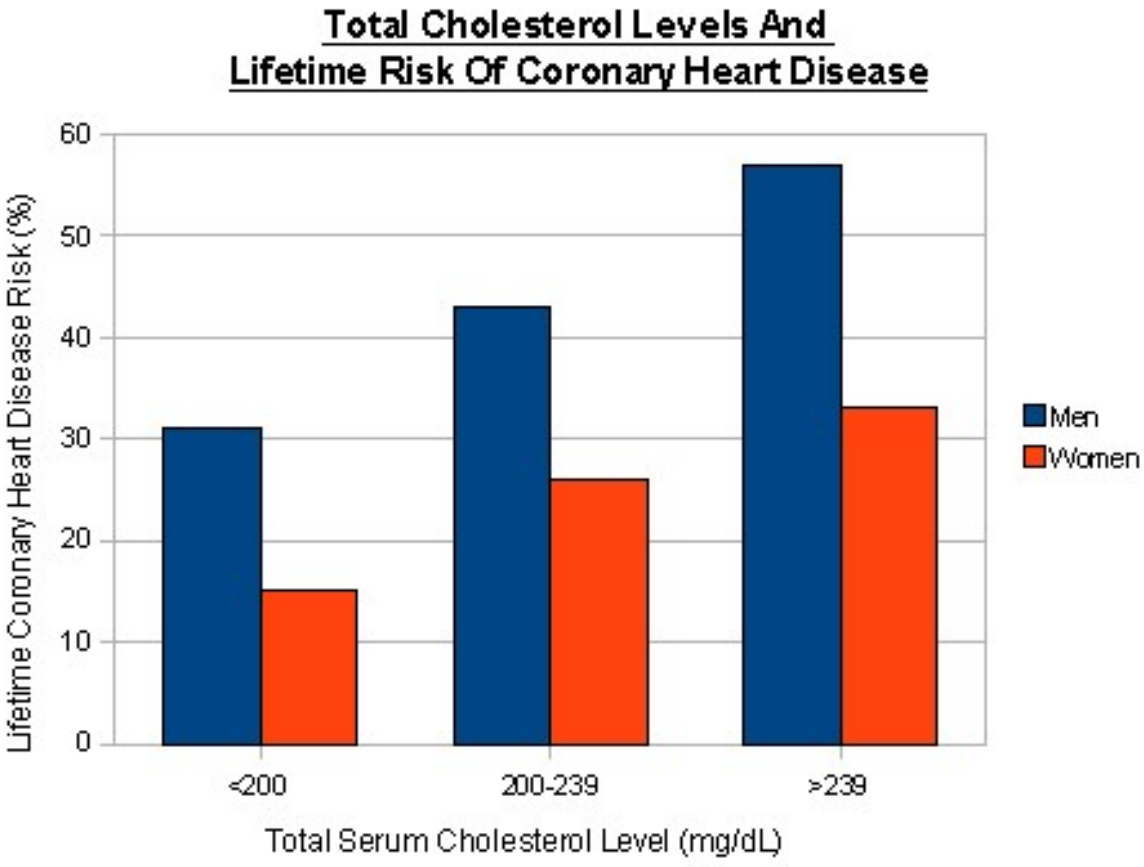
- Fibrous Plaques
- Smooth muscle cells migrate into the fatty streak, forms fibrous plaque
- Plaque begins to occlude artery
- Symptoms such as angina may start to occur

Third Stage

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

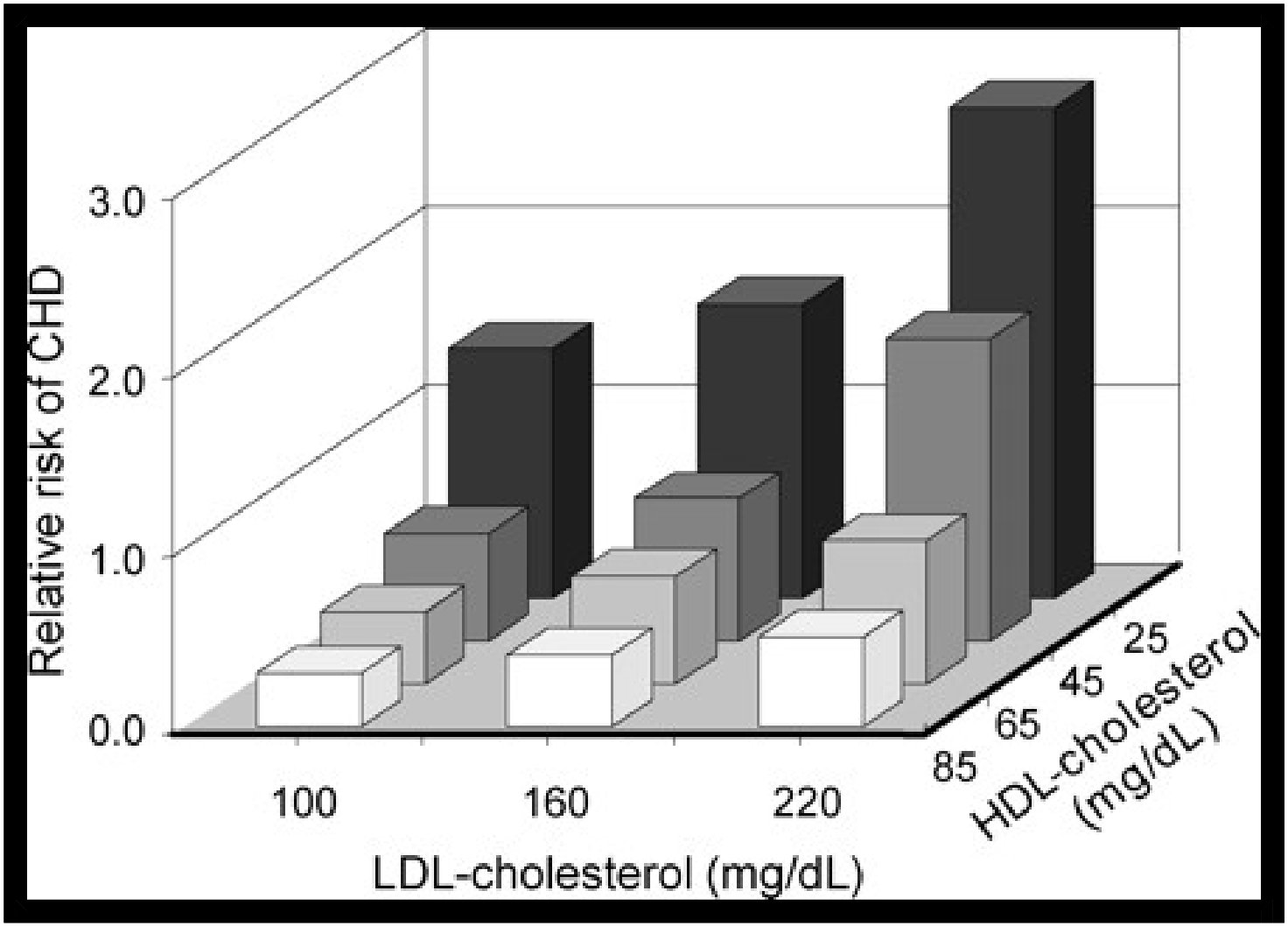
STAGES OF ATHEROSCLEROSIS





Source: "Lifetime Risk of Coronary Heart Disease by Cholesterol Levels at Selected Ages" - Archives of Internal Medicine, September 2003

Relationship Between LDL, HDL, and Coronary Heart Disease



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

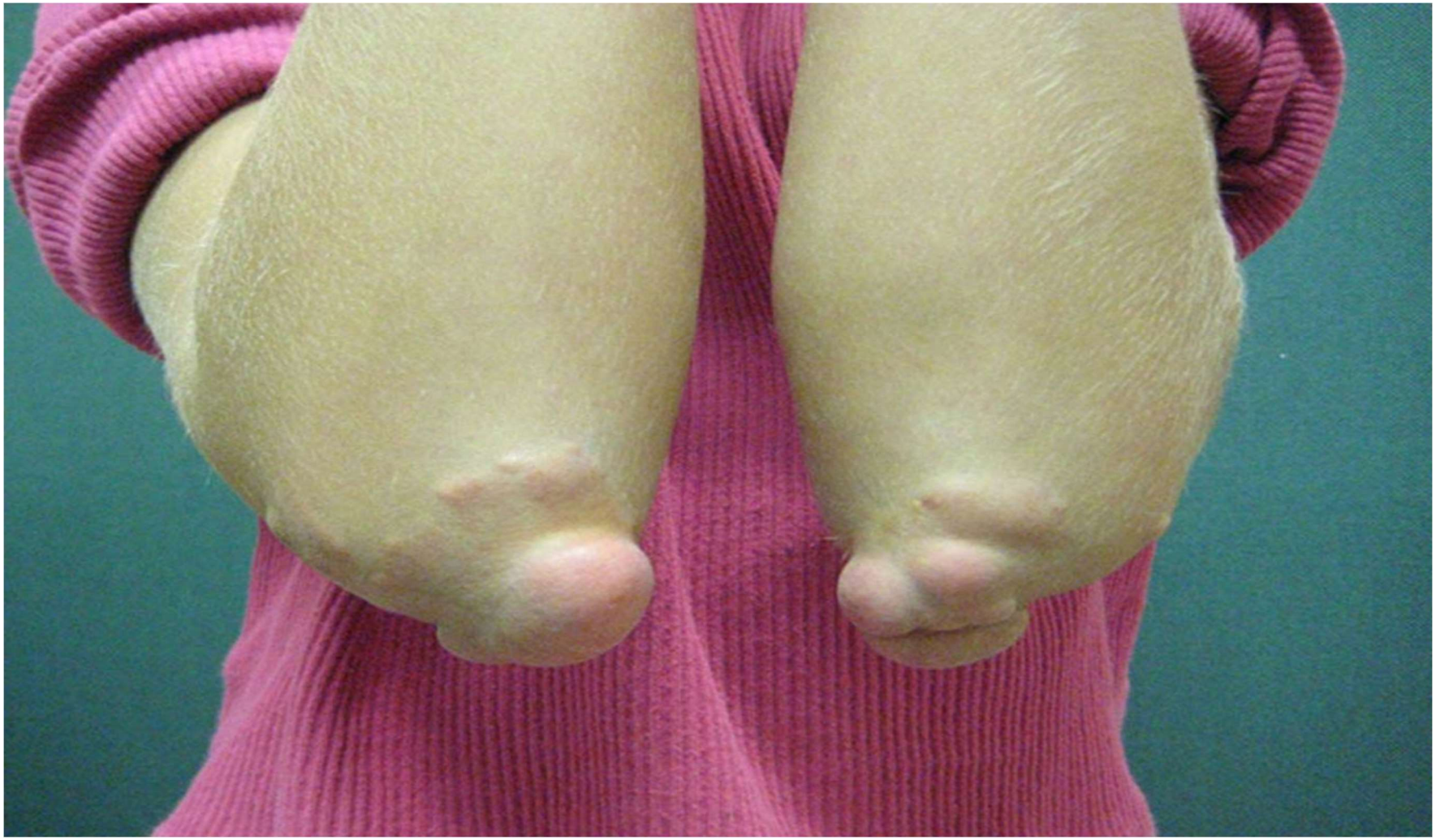
Lab Tests:

- ↑ 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)

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:

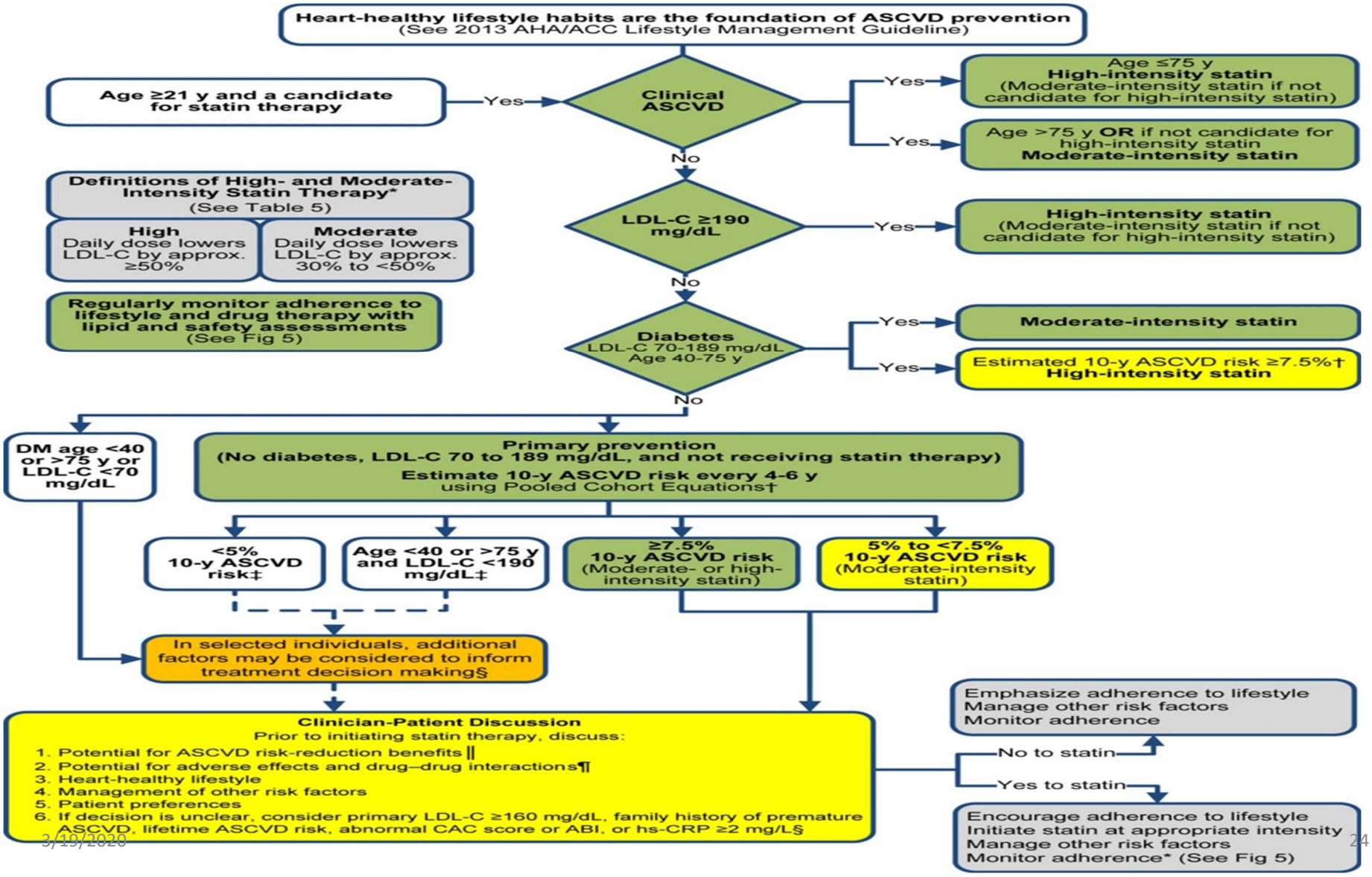
- total cholesterol and HDL-C
- systolic blood pressure
- diabetes
- smoking status

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

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

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

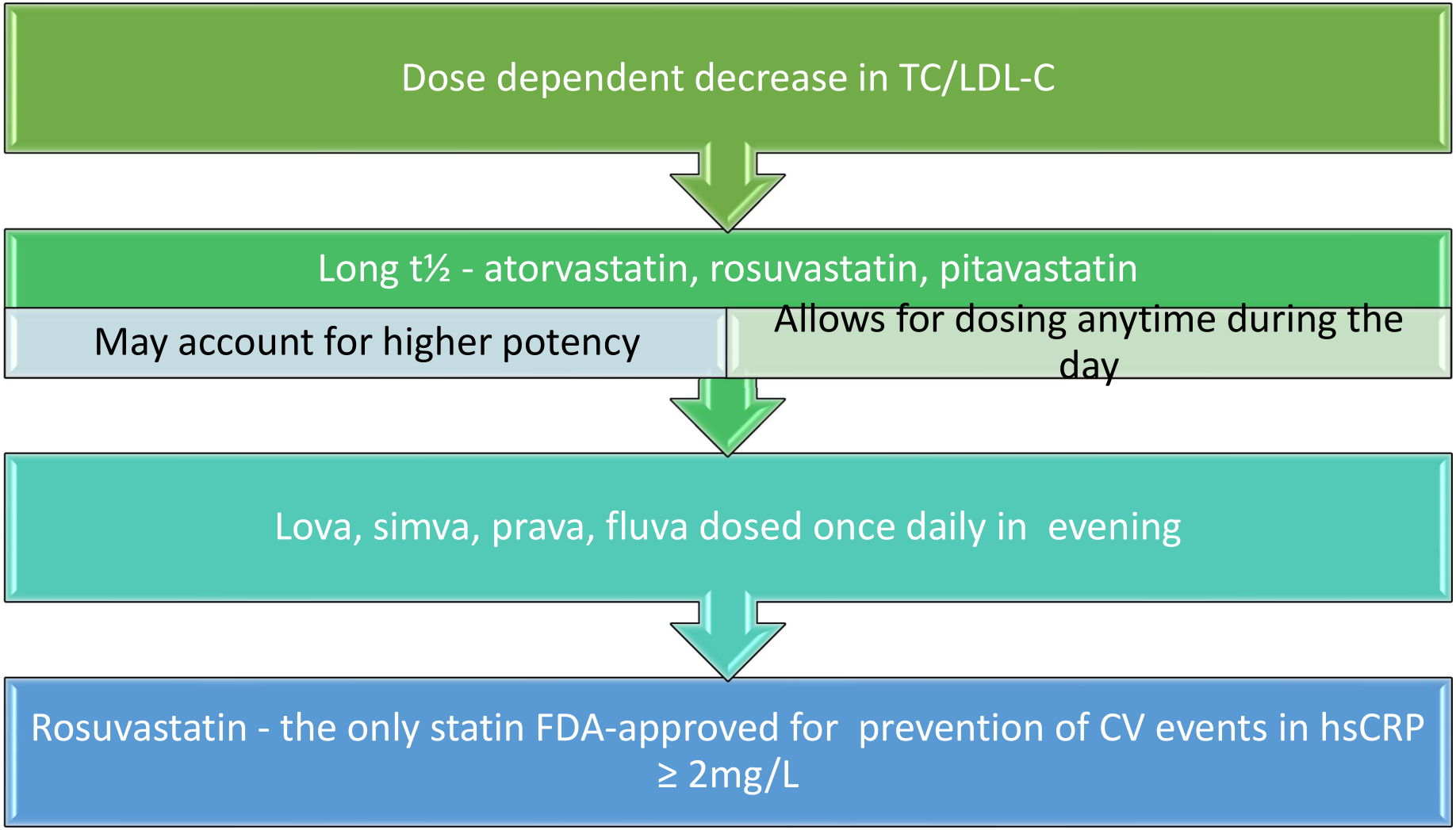
First-line therapy for LDL-lowering

Administered once daily – usually HS

Dose dependent decrease in TC/LDL-C

Contraindications – pregnancy, breastfeeding, active liver disease

HMG-CoA Reductase Inhibitors



Statin Pharmacokinetics

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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

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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

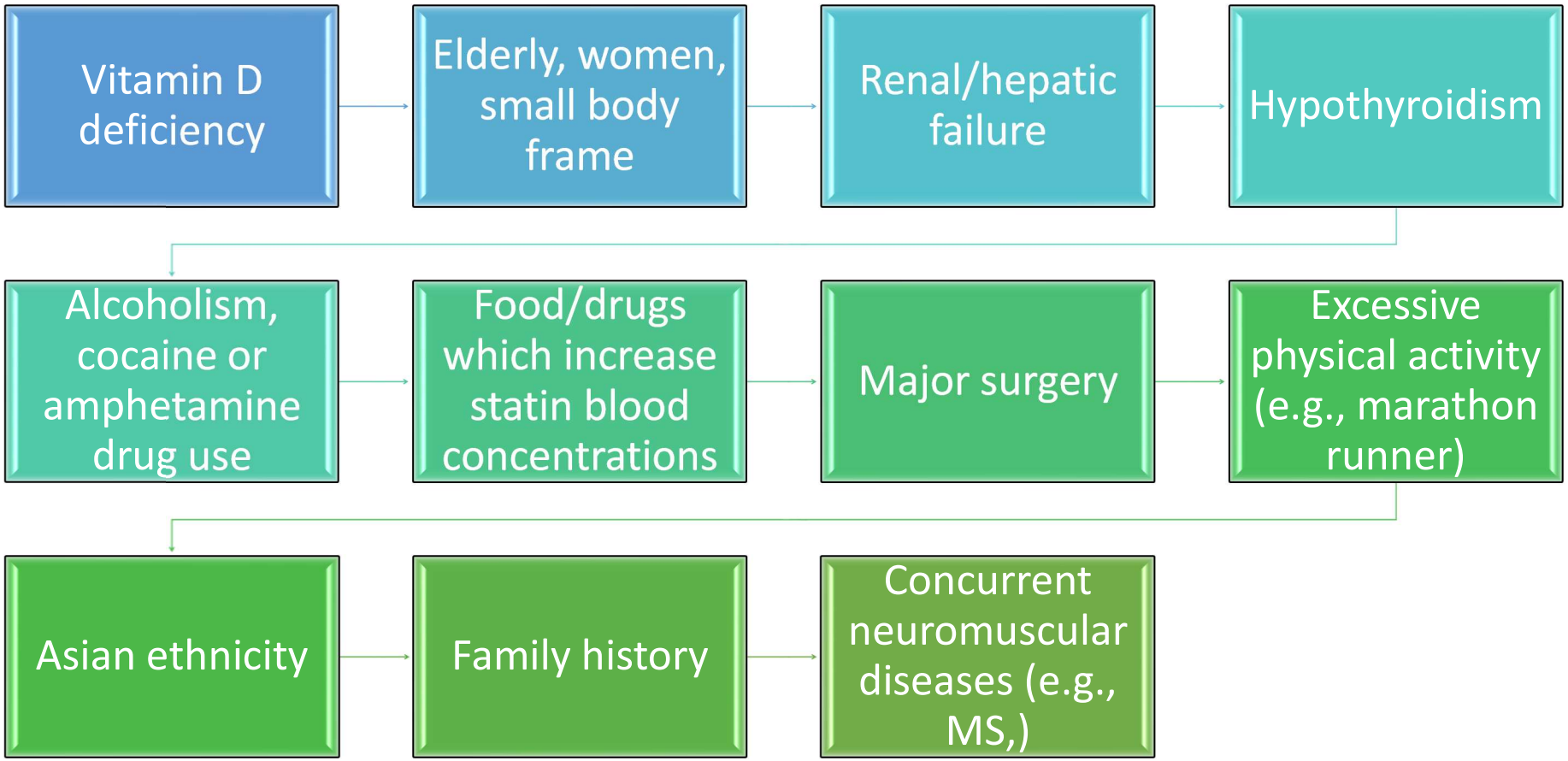
Rhabdomyolysis: muscle ache or weakness w/significant CK elevation

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

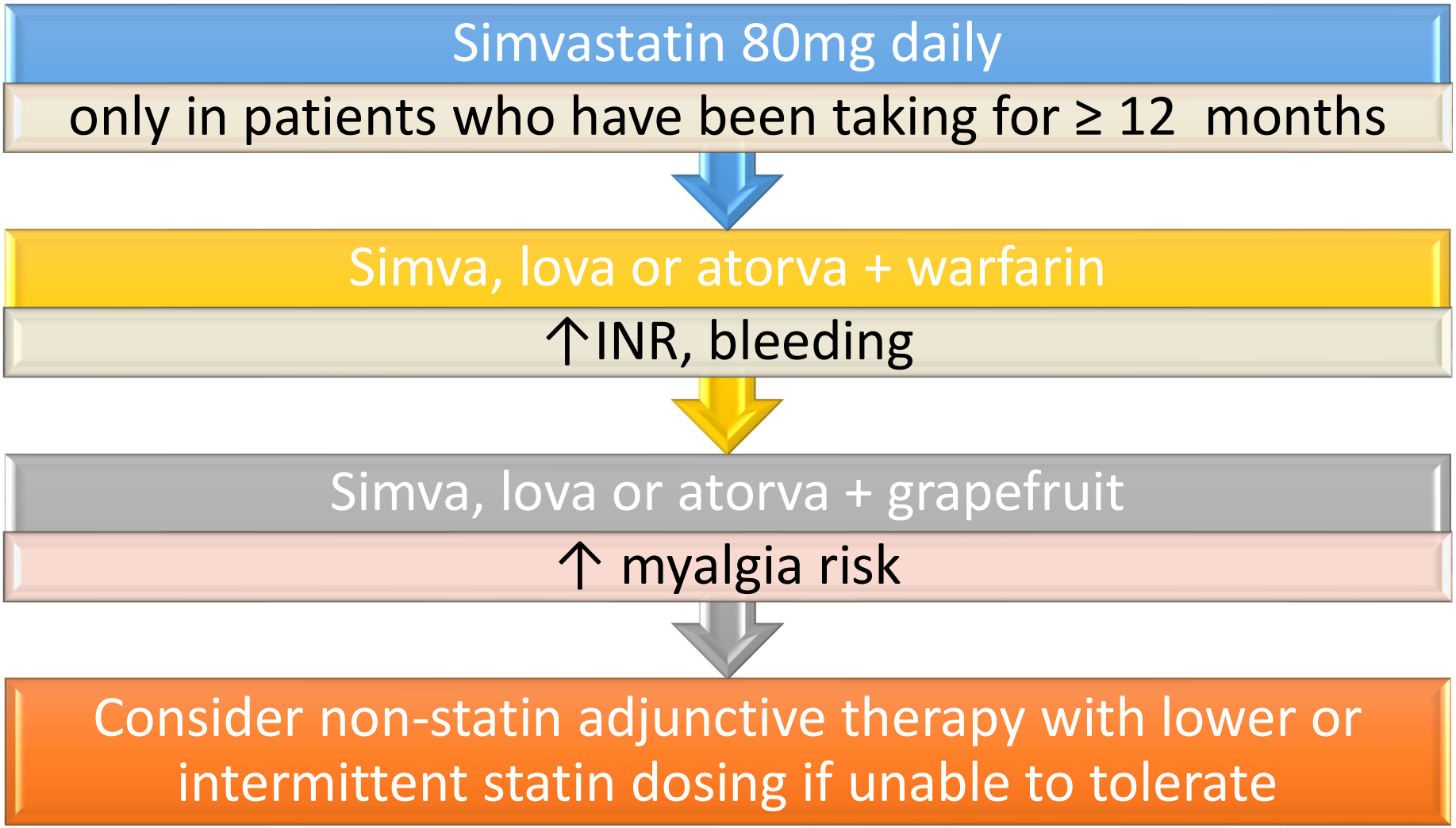
- Bleeding risk or male infertility

Cognitive impairment

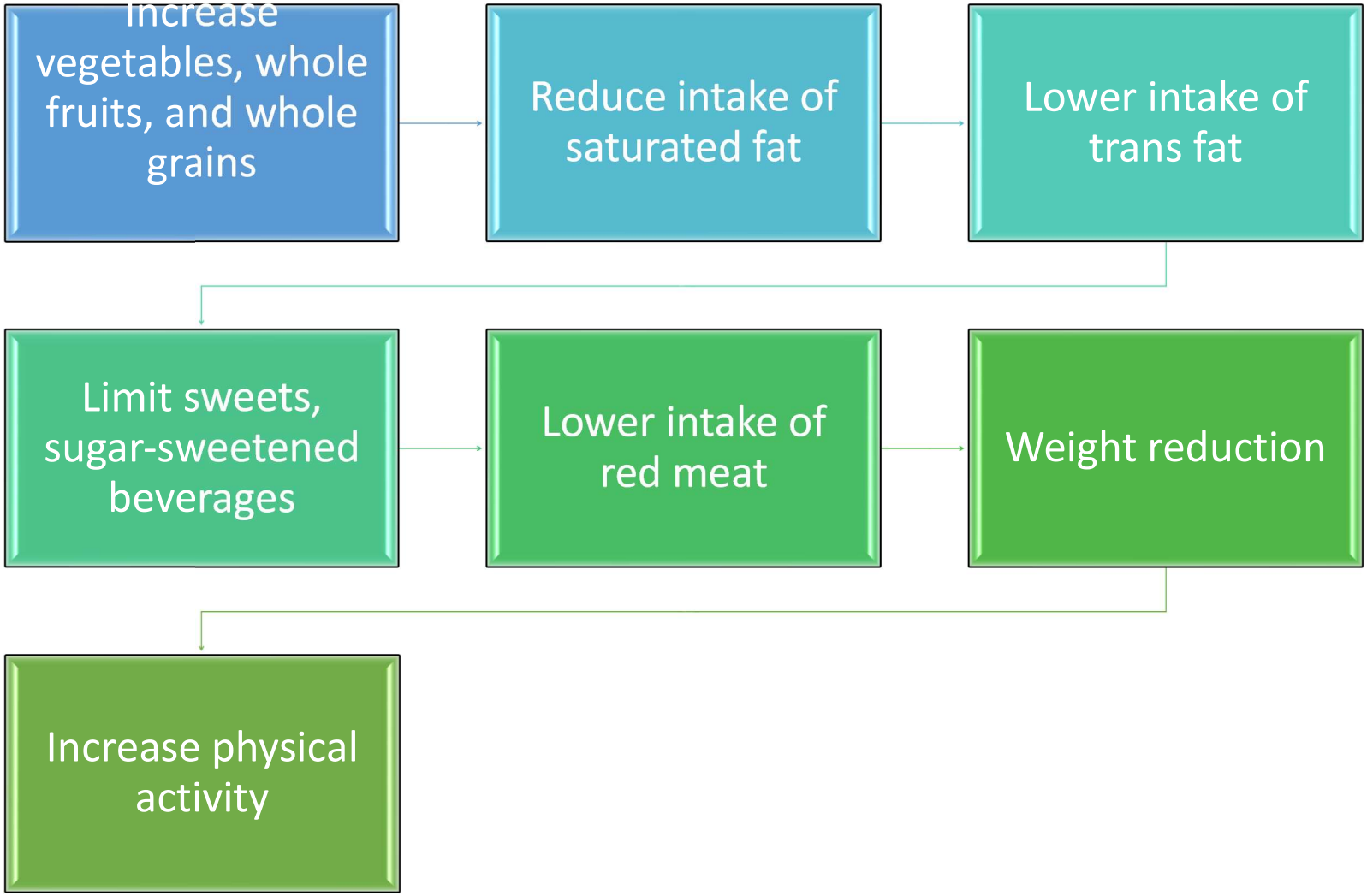
Relatively uncommon

- Memory loss or impairment
- Reversible upon discontinuation

Other Statin Recommendations



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

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)

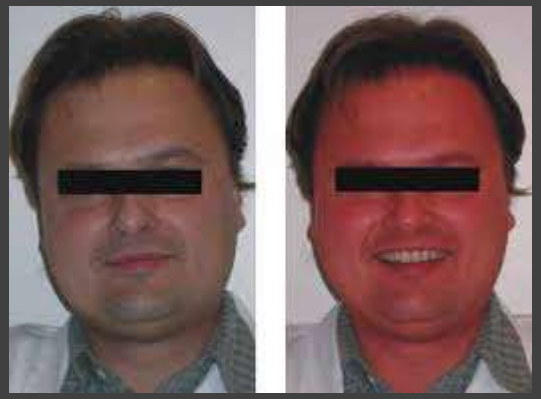
- Caution with statins - rhabdomyolysis (gemfibrozil)
- Gemfibrozil – contraindicated with simvastatin and repaglinide; avoid with statins if possible
- Potentiate effects of oral Vit K antagonists (gemfibrozil> fenofibrate)– monitor PT/INR closely
- Gemfibrozil safe for use during and after 2nd trimester
- Myalgia or myopathy risk

Statin-Fibrate Combination

Statin	Gemfibrozil	Fenofibrate
Atorvastatin	↑ in C_{max} (expected)	No change
Simvastatin	↑ in C_{max} by 2-fold	No change
Pravastatin	↑ in C_{max} by 2-fold	No change
Rosuvastatin	↑ in C_{max} by 2-fold	No change
Fluvastatin	No change	No change
Lovastatin	↑ in C_{max} by 2.8-fold	No change
Pitavastatin	↑ in C_{max} by 41%	Unknown

C_{max}, maximum concentration.

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

Tips for taking NIASPAN:

Take aspirin (up to the recommended dose of 325 mg) 30 minutes before you take NIASPAN to help reduce the frequency and severity of flushing. (Just check with your doctor first.)

Avoid alcohol, hot beverages (including coffee), and spicy foods near the time you take your NIASPAN to help reduce the chance of flushing.

Take NIASPAN at bedtime so flushing will most likely occur during sleep.

Take NIASPAN with a low-fat snack to lessen upset stomach.

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

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