Anti-Hyperlipidemia

- Red : important
- Black : in male / female slides
- Pink : in female's slides only
- Blue : in male's slides only
- Green : Dr's notes
- Grey: Extra information, explanation

OBJECTIVES:

By the end of this lecture, students should be able to :

✓Define hyperlipidemia vs normal lipid levels.

✓Discuss the non-pharmacological treatment of hyperlipidemia.

✓Classify lipid lowering agents targeting exogenous & endogenous pathways.

✓Expand on the pharmacology of drugs related to each group.

✓Hint on adjuvant drugs that can help in lipid lowering.

Editing File

Hyperlipidemia

- Is a major cause of atherosclerosis which may lead to coronary artery disease (CAD) and ischemic cerebrovascular disease
- Denotes abnormally ↑ levels of any/or all Lipids and/or Lipoproteins(LP) in blood

Origin of lipids

endogenous lipids: synthesized in liver.

exogenous lipids: ingested and processed in the intestine

The principle lipids in the blood are:

1. Cholesterol(C)
2. Triglycerides(TG)
3. Phospholipids(PL)
4. Non-esterified fatty acid(NEFA)
5. Cholesterol esters(CE)

Lipoproteins Classification:

They are classified into 5 families according to :
- The amounts of C, TG
- The types of apoproteins they contain

CM	VLDL	IDL	LDL	HDL
Chylomicrons	Very low density lipoproteins	Intermediate density lipoproteins	Low density lipoproteins	High density lipoproteins

Normal lipid levels:

C	<200 mg/dl
TGs	<220 mg/dl
LDL	<130 mg/dl **(BAD C)**
HDL	>50 mg/dl **(GOOD C)**

Lipids levels are detected in serum after a 12-hour fast

Factors promoting elevated blood lipids

1. **Smoking:** reduced levels of HDL,cytotoxic effects on the endothelium, increased oxidation of lipoproteins, and stimulation of thrombogenesis
2. **Family history of CAD**
3. **Diabetes Mellitus:** increase degeneration of VLDL and free fatty acids presented to the liver
4. **Hypertension**
5. **Obesity & Alcohol intake:** increases TGs
6. **Inactivity / lack of exercise**

Classification of Hyperlipidemia

Familial (hereditary) Hyperlipoproteinemia

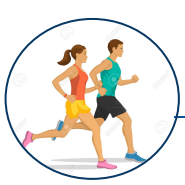
Which caused by elevated level of one lipid or lipoproteins as the following :

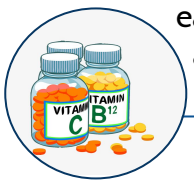
Class	Increased Lipoprotein	Risk
Type I	↑Chylomicron	-
Type IIa	↑LDL	↑
Type IIb	↑LDL and VLDL " mixed more dangerous "	↑
Type III	↑IDL	↑
Type IV	↑VLDL	↑
Type V	↑VLDL and Chylomicron	-

Therapeutic strategies for treatment of hyperlipidemia

A-Lifestyle changes


losing weight


regular exercise



eating adequate amount of antioxidant vitamins and use vegetable oils

healthy diet & optimal fat content

Stopping bad habits: Smoking, fast food and alcohol

Avoid trans-fatty acids

Lifestyle will reduce LDL-C by 8 to 15% but the long term compliance is a problem.

B-Antihyperlipidemic Drugs
classified According to:

Mechanism of Action

1-Inhibiting cholesterol absorption in the intestine.
eg. Ezetimibe

2-Sequester bile acids in intestine
eg. Exchange resins

3-Inhibiting cholesterol synthesis
eg. Inhibitors of hydroxymethylglutaryl coenzyme A reductase (Statins)

4-Alter relative levels and patterns of different plasma Lipoproteins
eg. Fibrates - Niacins (Nicotinic Acids)

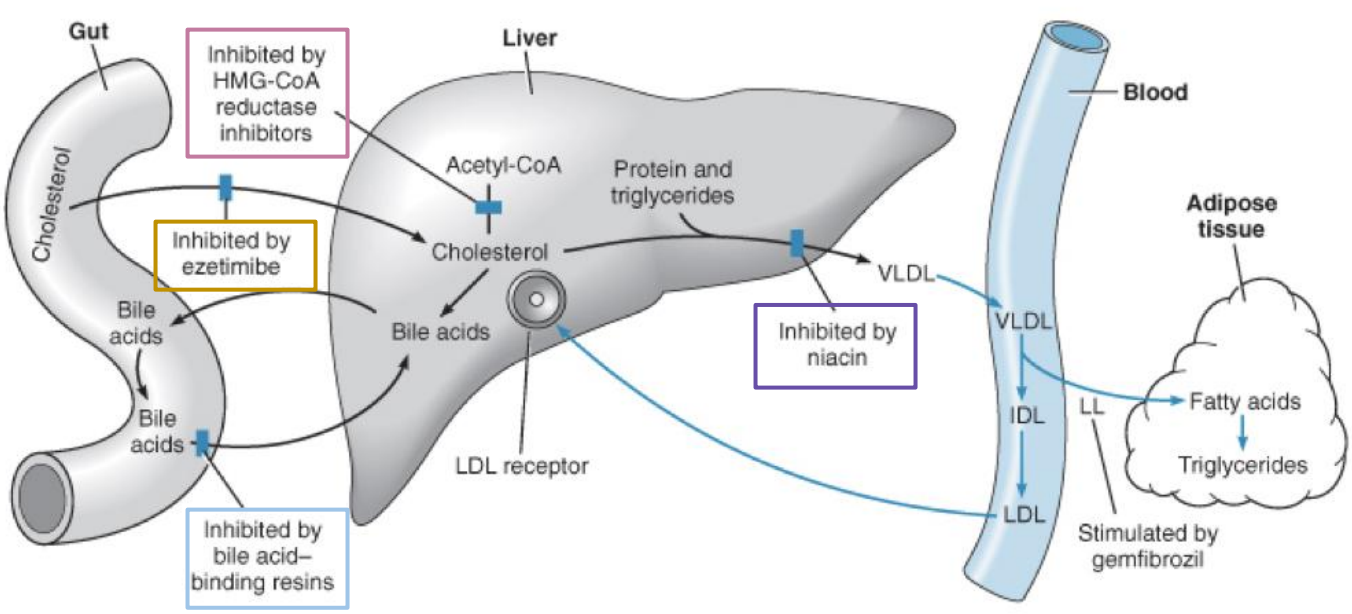
Site of Action

Agents targeting exogenous cholesterol
e.g - Ezetimibe
- Colestipol & cholestyramine

Agents targeting endogenous cholesterol
eg. -Statins
- Fibrates
-Nicotinic acid

Adjuvant agents
-Omega-3-Fatty Acids (fish oil)
-Stanols (nuts)

General Mechanism of Action of Antihyperlipidemic drugs



Agents Targeting Exogenous Cholesterol

1-Exchange Resins or Bile acid sequestrants

Drug	Cholestyramine	Colestipol	Colesevelam

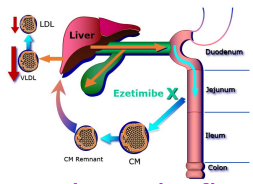
Overview ★	• Moderately effective with **excellent safety record.**
	• Large MW polymers which bind to bile acids and the acid-resin complex is excreted so their fecal excretion ↑ 10 folds
	  ○ prevents enterohepatic cycling of bile acids
	  ○ obligates the liver to synthesize replacement bile acids from cholesterol
	• The liver increases the number of LDL receptors to obtain more cholesterol thus:
	  ○ The levels of LDL-C in the serum are reduced as more cholesterol is delivered to the liver
	• **Excellent choice for people that cannot tolerate other types of drugs**		

M.O.A	• These drugs bound with bile acid and prevent their absorption and recycling so bile acid will be secreted in the feces • Bind to bile acids and bile salts in the small intestine • They form resin/bile acid (insoluble) complex which is prevent their reabsorption from the intestine • They disrupt the enterohepatic circulation of bile acids		
ADRs ★	• **They are clinically safe as they are not systemically absorbed** • GIT upset: abdominal discomfort, bloating, constipation • Decreased absorption of **fat** soluble vitamins (A, D, K) • **The concentration of HDL-C is unchanged**		
Contra-indications	• Complete Biliary obstruction (because bile is not secreted into the intestine) • Chronic constipation • **Severe hypertriglyceridemia** (TG >400 mg/dL) ○ The bile acid binding resins can raise triglycerides modestly (about 5%) and cannot be used if the triglycerides are elevated. First line drug to decrease LDLP, useless if there is high level of TGs, so used to treat LDLP when TGs is normal		
Interactions ★	• Interfere with the absorption of: **Statins, Ezetimibe, Chlorothiazide, Digoxin, Warfarin.** **Therefore, these drugs should be taken at least 1 hour before, or 4 hours after taking resins** • **Colesevelam** has not been shown to interfere with the absorption of co-administered medications and is a better choice for patients on multiple drug regimens		

Q: What is the drug that increase TGs? Ans:Resins

Agents Targeting Exogenous Cholesterol

2-Cholesterol Absorption Inhibitors

Drug	Ezetimibe
M.O.A	• Blocks C transporter located on brush border of small intestine→ ↓pool of C available to the liver→ upregulate LDL receptor, trapping more LDL particles from blood.  • 1-Ezetimibe reduces C absorption. Therefore, ezetimibe reduces the flux of C from the intestine to the liver. 2-Because this C is packaged and resecreted by the liver into the blood as VLDL (precursor of LDL in plasma), reduced flux of C to VLDL particles will lower LDL-C.
Pharmaco-logical actions	↓LDL 20% ↓TG 8% , ↑HDL 1-4% No effect on steroids, lipid-soluble vitamins, bile acids
P.K	• Absorbed & conjugated in intestine to active glucuronide • Reaches peak blood level in 12–14 hours • Undergoes enterohepatic circulation • Its half-life is 22 hours • Most of the drug is excreted in feces
Clinical Uses	**As Monotherapy:** Primary prevention of low risk of CHD which needs modest↓ LDL (if LDL is very high, statins should be used. Ezetimibe isn't used alone except in modest of LDL) **As Combination Therapy; it's safe With:** • **statins**; synergistic In moderate/severe ↑ LDL • Or If must ↓ statin dose because of side effects • Or with other lipid lowering drugs **As fibrates**
ADRs	**Not common** • GIT disturbance (the main symptoms for most of antihyperlipidemics) • headache, fatigue, arthralgia and myalgia

statins with ezetimibe is a good combination because ezetimibe will work in exogenous while statins in endogenous cholesterols

HMG-CoA Reductase Inhibitors (Statins)

- Hydroxy MethylGlutaryl-Coenzyme A reductase (HMG-CoA) inhibitors or strains **are the most effective and best-tolerated agents for treating hyperlipidemia.** "most important types of drugs"
- Statins are considered as first-line drugs when LDL-lowering drugs are indicated Statins are the best LDL lowering drugs with raising HDL effect.

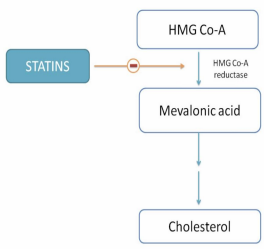
Preparation:

Rosuva-statin · Atorva-statin · Simva-statin · Prava-statin · Lova-statin

these can be used alone or with other anti-hyperlipidemic drugs (ezetimibe) for treatment of drug resistant dyslipidemia.

Mechanism of Action of Statins

Statins are potent competitive inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, which catalyzes an early, rate-limiting step in do-novo hepatic C synthesis. Thus, HMG-Co A is not converted to mevalonic acid



1- Statins lower blood C levels by inhibiting de novo hepatic C synthesis

2-The liver compensates by ↑ the number of LDL receptors on the surface of hepatocytes (upregulation of LDL- R)

3-This results in ↑removal of LDL from the blood and lowering of serum LDL- C levels

4-Because C is required for the synthesis of (the precursor of LDL-C), production of VLDL ↓

Effects of Statins

Pleiotropic Effects:

You have to know the meaning of "pleiotropic" which mean additional.

- Antioxidant effect
- Improved endothelial function
- Stabilization of atherosclerotic Plaque
- Reduced inflammatory state
- Antithrombotic actions
- Cardioprotection
- Stroke protection

Main Effect:

- Statins cause modest ↓ in plasma TG and slight ↑ in HDL-C
- Cholesterol biosynthesis reduction
- ↓ TG , ↓LDL ,↓total cholesterol ,↑HDL

Agents Targeting Endogenous Cholesterol

1-Statins

P.K

- Most statins have a high first pass clearance by the liver.
- Greater than 95% of most of these drugs are bound to plasma proteins" rise drug drug interactions " with short half-life.
- Drug-drug interactions involve specific interactions with the cytochrome P450 drug metabolizing system **especially CYP3A4.** " drug with same mechanism or CYP3A4 have more chance to develop drug drug interactions"
- All statins are taken orally **at bedtime** because of hepatic C synthesis is maximal between midnight and 2:00 am **except atorvastatin** taken at any time because of its long half-life (14 hours).

Indications

As monotherapy;

- **Secondary Prevention** In all ischemic insults [stroke, AMI ...etc] So given from 1st day of ischemic attack.

- **Primary Prevention:**

1. Patients with hyperlipidemia and with other risks for ischemic insults.
2. Type IIa Hyperlipoproteinemia , If no control→combine (sequestrants ezetimibe, niacin) to decrease C.

As Combination therapy:

- Mixed dyslipidaemias added to fibrates or niacin if necessary.

★ In diabetics and patients with insulin resistance [metabolic syndrome] because these patients will possess small dense LDL (severely atherogenic) + evident endothelial dysfunction + increased thrombotic profile.

ADRs ★

1. Common side effects: Headache, **myalgia** ,fatigue, GI intolerance and flu-like symptoms.
2. Hepatotoxicity raised concentrations of liver enzymes (serum aminotransferases). "you have to check lipid profile every 6 month"
3. **Myopathy** (increased creatine kinase [CK] released from muscles)
4. Teratogenicity ,statins should be avoided during pregnancy

Inter-actions ★

- **Statins potentiate the action of oral anticoagulant and antidiabetic drugs (by displacement from plasma protein binding sites).** "The effect of drug will increase because it's become free"

- **Drugs that increase the risk of statin induced myopathy include**

1. **Other antihyperlipidemics (fibrates).**
2. Drugs metabolized by 3A4 isoform of cytochrome P450: erythromycin, verapamil so hypertensive patients are liable to get myalgia with statin,cyclosporine, ketoconazole.

Q:Which drugs is beneficial with verapamil ? " verapamil as example"

- Pravastatin and fluvastatin are the statin of choice in patients taking other drugs metabolized by cytochrome 3A4 system.

Statin induced myopathies

muscle aches soreness or weakness associated with an elevation of creatine kinase (CK) are the best indicator of statin induced myopathy

Statin induced myopathy

Failure to recognize myopathy and to discontinue drug therapy, this lead to:

- rhabdomyolysis
  - Severe muscle injury, myoglobin released in circulation and riches kidney causing renal failure
- myoglobinuria
- acute renal necrosis

Elevation of serum transaminase

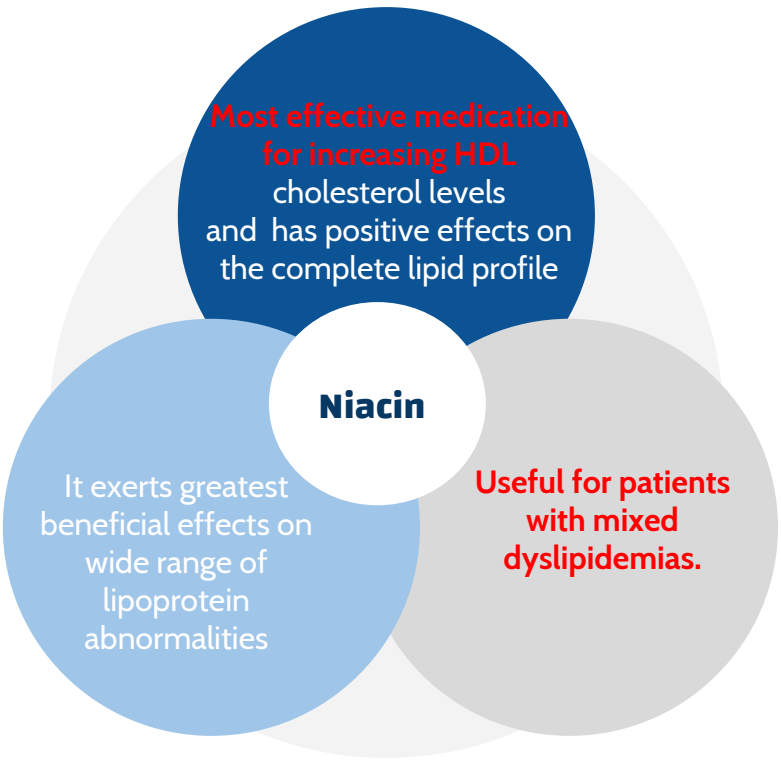
- Can progress to evident hepatotoxic
- so, lab investigations are recommended every 6 months
- IF level ↑3 folds, statin must be stopped then adjust the dose

Elevation of creatine kinase activity (index of muscle injury)

- measured only if myalgia or myositis develops
- If it is up to 3-5 folds we decrease statin doses
- OR omit (prevent) combination with fibrate

Niacin (Nicotinic Acid):

Is Water soluble B-complex vitamin **with multiple actions**



Agents Targeting Endogenous Cholesterol

2-Niacin (Nicotinic Acid)

M.O.A

In adipose tissue:

- It binds to adipocytes **nicotinic acid receptors** this will lead to decrease in free fatty acids mobilization from adipocytes to the liver resulting in ↓ TG and thus VLDL synthesis.

In liver:

- Niacin inhibits hepatocyte 2-diacylglycerol acyltransferase a key enzyme for TG synthesis. Thus it decreases VLDL production (decreased TG synthesis and esterification).

In plasma:

- It increases Lipoprotein lipase(LPL) activity that increases clearance of VLDL chylomicron.

Pharmaco-logical actions

Effect on ↓VLDL by:

1. ↓synthesis in liver
2. increased clearance in plasma
3. ↓mobilization of free fatty acids from adipose tissue

Effect on↓ LDL:

- due to reduction of its precursor (VLDL).

Effects on ↑HDL by :

- Induces modest increase in HDL-C (The catabolism of HDL can be inhibited by nicotinic acid through a mechanism that is largely unknown)

- Niacin also promotes hepatic apoAI production and slows hepatic clearance of apoA-I and HDL. →Q :How niacin increase HDL ?

Clinical Uses

As monotherapy or in combination with fibrate, resin or statin.

- Type IIa ,IIb hypercholesterolemia & any combined hyperlipidemia.
- Patient with hypertriglyceridemia & low HDLC

ADRs

- The most common side effect is cutaneous flushing (which is prostaglandin-mediated, can be avoided by aspirin ½ hour before niacin).
- **GIT disturbances:**
  Dyspepsia, nausea, vomiting, reactivation of peptic ulcer (can be decreased if taken after meal)
- **High doses:**
  -Reversible ↑ in liver enzymes → hepatotoxicity.
  -Impairment of glucose tolerance → overt diabetes
  -↑ uric acid → gout

Contra-indications

- Gout
- Peptic ulcer
- Hepatotoxicity
- Diabetes mellitus (used with caution)

Agents Targeting Endogenous Cholesterol

3-Fibrates

Drugs	Clofibrate (Rarely used, carcinogenic and cause gallbladder stones)	Gemfibrozil	Fenofibrate
M.O.A	• They are agonist of peroxidase proliferator activated receptors (PPARα) which is intracellular receptor "Nuclear receptor" that modulate fat metabolism. • So, they increase gene transcription of **lipoprotein lipase(LPL)** leading to increased catabolism of TG in VLDL and chylomicrons.		
Pharmaco-logical actions	• ↑LPL activity which increases clearance of VLDL & chylomicron in plasma. • A marked **reduction in TG** (due to stimulation of catabolism of VLDL). • ↑FFA uptake by the liver. • ↑LDL-C uptake by the liver. • ↑ **in HDL-C** (by increasing the production of the apoprotein components of HDL). • ↑ **excretion of hepatic C in bile**, thus endogenous hepatic C synthesis may be decreased.		
Clinical Uses	1st-line defense for: • mixed dyslipidemia (i.e. raised serum TG and C). • Patients with low HDL and high risk of atheromatous disease (often type 2 diabetic patients). • Patients with severe treatment- resistant dyslipidemia (combination with other lipid-lowering drugs).		
ADRs	• **Gallstones: Clofibrate increases C content of bile, predisposes to gallstones and its use is therefore limited to patients who have cholecystectomy or biliary tract disease** • GIT indigestion ,abdominal pain ,diarrhea. , headache ,fatigue,weight gain • Rash, urticaria, hair loss. • **Myositis: can occur resulting in weakness and tenderness of muscles (if left untreated may lead to Rhabdomyolysis→Acute renal failure),** this occurs in: ○ If combined with statins (each –ve metabolism of other) ○ In alcoholics ○ In impaired renal function.		
Inter-actions	• **Increased risk of myopathies when used with statins,** they↓metabolism of statins = toxicity myalgia, myositis,...etc. so we Give lower doses • They displace drugs from plasma proteins (oral anticoagulant like warfarin, oral hypoglycemic drugs).		
Contra-indications	• Impaired renal function. • Pregnant or nursing women. • Preexisting gallbladder disease.		

Which drug increases HDL ? Niacin
Which class of drug causing gallstones ? Fibrates
Which is better to diabetic patient statin or fibrate ? statin due to pleiotropic effects

Drug class	Agents	Effect (% change)	Side effects
HMG CoA reductase inhibitors	Lovastatin Pravastatin	**↓LDL (18-55),** ↑ HDL (5-15) **↓ triglycerides (7-30)**	• Myopathy • increased liver enzymes
Cholesterol absorption inhibitors	Ezetimibe	↓ LDL(14-18), ↑ HDL (1-3) ↓triglyceride (2)	• Headache • GI distress
Nicotine's acid		**↓LDL (15-30),** **↑HDL (15-35)** **↓Triglyceride (20-50)**	• Flushing • Hyperglycemia • Hyperuricemia • Git distress • Hepatotoxicity
Fibric acids (Fibrate)	Gemfibrozil Fenofibrate	**↓LDL (5-20),** ↑HDL (10-20) **↓Triglyceride (20-50)**	• Dyspepsia • Gallstones • myopathy
Bile acid sequestrants	Cholestyramine	↓ LDL ↑ HDL **↑ triglycerides** "Q: if you give a patient drug and TG increase what is the drug ?"	• GI distress, • constipation, • decreased absorption of other drugs

Adjuvant Therapy in Hyperlipidemia

Drug	Omega 3 FA	β-Sitosterol
Pharmacological actions	**It will decrease (TG) by:** -decreasing the enzymes involved in TG synthesis. - increasing beta oxidation of FFA **provide some vascular protection by:** -decrease platelet function. -Prolongation of bleeding time. -Anti-inflammatory effect.	Compete with dietary and biliary C absorption leads to decrease LDL levels 10%
Indication	Approved as adjunctive for treatment of very high TGs	Given as food supplement before meal in hypercholestrolemia
Found in	Fish oil.	in plants with similar structure as Cholesterol (C).

Anti hyperlipidemic combinations

Female slides only

Indications:

-Severe hypertriglyceridemia or hypercholesterolemia
-To take lower doses of each drug
-High LDL or VLDL not normalized with a single drug.

Combinations:

Use:
Statin & ezetimibe
Don't Use:
-Resins with statins or ezetimibe
-Statins & Fibrates : if forced ,use not more than ¼ maximum dose of statin and use pravastatin

QUIZ

MCQ

1- Which of the following is the most common adverse effect of Anti-Hyperlipidemia drug therapy?

A-Elevated blood pressure B-Gastrointestinal disturbance C-Neurological problems

2- Which one of the following drugs decreases cholesterol synthesis by inhibiting the enzyme hydroxymethylglutaryl coenzyme A reductase?

A-Fenofibrate B-Cholestyramine C-Lovastatin

3- A 65-year-old man has type 2 diabetes mellitus and an LDL-C of 165 mg/dL. Which is the best option to lower LDL-C and decrease the risk of ASCVD events in this patient?

A-Fenofibrate B-Colesevelam C-Rosuvastatin

4- which patient population is most likely to experience myalgia or myopathy with use of HMG CoA reductase inhibitors?

A-patients with renal insufficiency B-Patients with gout C-Patients with hypertriglyceridemia

1-B 2-C 3-C 4-A

SAQ

1-JS is a 65-year-old man who presents to his physician for management of hyperlipidemia. His most recent lipid panel reveals an LDL cholesterol level of 165 mg/dL. His physician wishes to begin treatment to lower his LDL cholesterol levels.Which drug is the best option to lower JS's LDL cholesterol levels?

2-WW is a 62-year-old female with hyperlipidemia and hypothyroidism. Her current medications include cholestyramine and levothyroxine (thyroid hormone). What advice would you give to WW to avoid a drug interaction between her cholestyramine and levothyroxine?

3-CN is a 72-year-old male who is treated for hyperlipidemia with high-dose atorvastatin for the past 6 months. He also has a history of renal insufficiency. His most recent lipid panel shows an LDL cholesterol level of 131 mg/dL, triglycerides of 510 mg/dL, and HDL cholesterol of 32 mg/dL. His physician wishes to add an additional agent for his hyperlipidemia. Which drug is the best option to address CN's dyslipidemia?

4-AJ is a 42-year-old man who was started on niacin sustained-release tablets 2 weeks ago for elevated triglycerides and low HDL levels. He is complaining of an uncomfortable flushing and itchy feeling that he thinks is related to the niacin. What is the option that can help AJ manage this adverse effect of niacin therapy?

Q1.Simvastatin Q2.Take levothyroxine 1 hour before cholestyramine Q3.Niacin Q4.Taking aspirin 1⁄2 hour before niacin

pharmacology

Team 438

GOOD LUCK

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Share with us your ideas !