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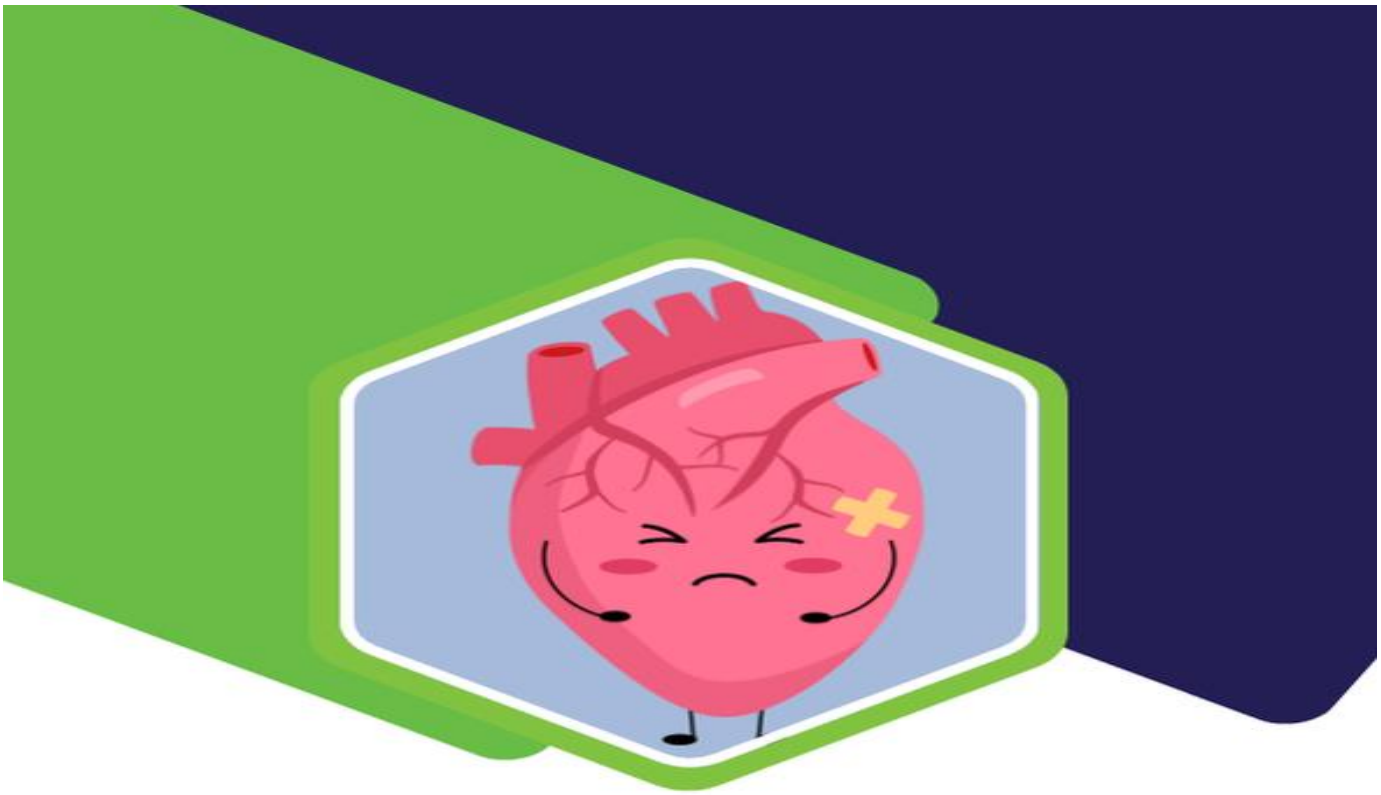


Dyslipidemia

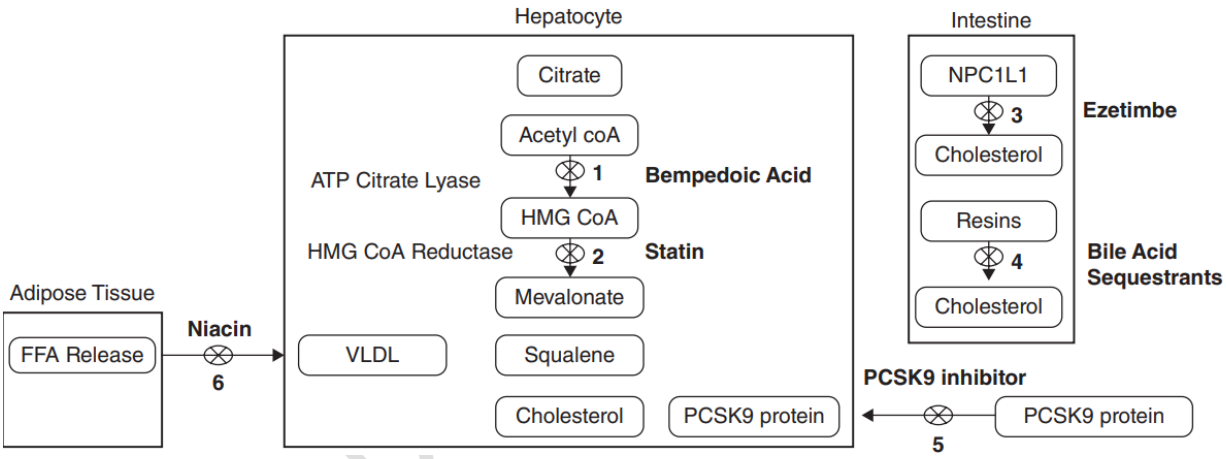
DR .TASNEEM

connect on : join to facebook group
(therapy1) Dr.tasneem

قاتِل حتى لا يستخدمك أحدهم في سبيل تحقيق حلمه

Dyslipidemia -part2

-Pharmacotherapy



▶ Statins (HMG-CoA Reductase Inhibitors)

the preferred LDL-lowering medications.

MOA: inhibit conversion of HMG-CoA to L-mevalonic acid and subsequently cholesterol

EX: Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Pitavastatin, Rosuvastatin, Simvastatin.

-statins lower LDL cholesterol levels by approximately 21% to 63% , are moderately effective at reducing triglycerides, and modestly raise HDL cholesterol.

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-Statins are routinely recommended to take **in the evening** as that is when the body produces the most cholesterol(most important for statins with shorter half-lives, but those with a long half-life [eg, atorvastatin, rosuvastatin] can be taken **any time of day**)

-it is has also (pleiotropic effects) such as such as reducing lipoprotein oxidation, enhancing endothelial synthesis of nitric oxide, and inhibiting **thrombosis**

S.E: Elevations in liver function tests (LFTs), statin-associated muscle symptoms (SAMS) (including myalgia, myopathy, and rhabdomyolysis)

-Statins should be dose reduced and/or discontinued promptly if serum transaminase levels (liver function tests) rise to three times upper limit of normal or if patient develops signs or symptoms of myopathy.

-LFTs should be obtained at baseline

-Myalgia is defined as muscle aches or pains not associated with creatine kinase (CK) elevations.

-Myopath: defined as unexplained muscle weakness or pain associated with CK elevations greater than 10 times the upper limit of normal.

-Rhabdomyolysis: defined as muscle symptoms with marked elevation in CK of at least 40 times the upper limit of normal and creatinine elevation usually associated with myoglobinuria and brown urine

مو اي مريض بياخد ستاتين بصير عنده الم العضلات هاد في ريسك فاكتور ..يلي هم :

The risks associated with statin-induced myopathy include:

- Small body frame and frailty.
- Multisystem disease (eg, CKD, especially due to DM).
- Perioperative periods.

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• Multiple medications (see next bullet).

• Specific concomitant medications or consumptions (fibrates (especially gemfibrozil, but other fibrates too), nicotinic acid (rarely), cyclosporine, azole antifungals, macrolide antibiotics, protease inhibitors, nefazodone, verapamil, amiodarone, large quantities of grapefruit juice , and alcohol abuse.

how to manage SAMS?

It is reasonable to check a baseline CK in patients at risk for myopathy.

1-Follow-up CK(in patients complaining of muscle pain, weakness, tenderness, or brown urine)

2-ruled out secondary causes of muscle symptoms((eg, vitamin D deficiency, hypothyroidism, muscle disorders)

3-if their CK is greater than three times the upper limit of normal but less than 10 times, they can continue their statin therapy if mild symptoms and repeat a CK in 1 week after that if the CK is decreasing or stable, they can be continued on their statin and continue to monitor for muscle symptoms, but if CK is increasing, then the statin should be stopped and the CK reassessed when the patient's symptoms have resolved.

4-If CK is greater than 10 times the upper limit of normal, they should immediately have their statin stopped and be instructed to increase their fluid intake

5-If the CK is greater than 40 times the upper limit of normal, they would meet the definition of rhabdomyolysis and should immediately go to the hospital to be assessed as they are at a high risk of acute renal failure

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كتبتلكم الحالات يلي عندها منوقف الدوا غير هيك اي قراءة او ارتفاع او انخفاض بيقدر يكمل المريض دواه

Patient assessment for symptoms of myopathy should be done 6 to 12 weeks after starting or changing therapy and at each visit.

ممكن الستاتين يرفع شوي السكري ويعمل مشاكل بضعف الادراك وغيرها بس هالشي بروح لما نوقف الدوا

-the other statins **except**(pravastatin and pitavastatin):

undergo biotransformation by the cytochrome P-450 (CYP) system with lovastatin and simvastatin having the highest risk of drug–drug interactions so avoid statin metabolism inhipitor

-**don't give statin with cyclosporine and gemfibrozil** : they inhibit drug transporters in the gut and liver that can increase statin concentrations

-The time until maximum effect on lipids for statins is generally 4 to 6 weeks

▶ Cholesterol Absorption Inhibitors:

Ex: Ezetimibe

MOA: blocks biliary and dietary cholesterol as well as phytosterol (plant sterol) absorption by interacting with the NPC1L1transporter

-Ezetimibe reduces LDL cholesterol by an average of 18%.

-Ezetimibe lowers triglycerides by 7% to 9% and modestly increases HDL cholesterol

-Ezetimibe is contraindicated in patients with active liver disease or unexplained persistent elevations in LFTs.

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- Ezetimibe combined with simvastatin was shown to further reduce ASCVD events in patients who have suffered a recent MI compared to simvastatin alone.

- ezetimibe combined with bempedoic acid has been shown to be safe and effective at lowering LDL cholesterol.

-Ezetimibe is primarily used in combination with a statin when adequate reductions in atherogenic cholesterol are not achieved or in those patients who are intolerant to statin therapy

-The time until maximum effect on lipids for ezetimibe is generally 2 weeks.

▶ Bile Acid Sequestrants

Ex: Cholestyramine, Colesevelam ,Colestipol

MOA : Resins are highly charged molecules that bind to bile acids in the gut The resin–bile acid complex is then excreted in the feces.

-**Resins are moderately effective in lowering LDL cholesterol but do not lower triglycerides**. Moreover, in patients with elevated triglycerides, the use of a resin may increase triglycerides.

-Resins reduce LDL cholesterol from 15% to 30%, with a modest increase in HDL cholesterol (3%–5%)

-Resins are most often used as adjuncts to statins in patients who require additional lowering of atherogenic cholesterol and are an option to add to statins if ezetimibe and PCSK9 inhibitors are not an option.

-they are an option to lower LDL cholesterol in patients who are completely statin intolerant or cannot tolerate a moderate or high dose of statin and need further LDL-cholesterol lowering

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S.E: cholestyramine or colestipol report constipation and symptoms such as flatulence and bloating

-Resins should be started at the lowest dose and escalated slowly

-Patients should be instructed to prepare the powder formulations in 6 to 8 ounces (approximately 180–240 mL) of noncarbonated fluids, usually juice (enhances palatability) or water.

-Colesevelam is better tolerated with fewer GI side effects, although it is more expensive.

-Colesevelam also has an indication for improvement of glycemic control in type 2 DM.

-All resins have the potential to prevent absorption of other drugs such as digoxin, warfarin, thyroxine, thiazides, β-blockers, fatsoluble vitamins, and folic acid.

Potential drug interactions can be avoided by taking a resin either 1 hour before or 4 hours after these other agents.

The time until maximum effect on lipids for resins is generally 2 to 4 weeks.

▶ Adenosine Triphosphate Citrate Lyase Inhibitors:

Ex: Bempedoic acid

S.E : Hyperuricemia

Bempedoic acid decreases LDL cholesterol

Bempedoic acid reduces LDL cholesterol by an average of 15% to 25% and up to 38% when combined with ezetimibe

combination of bempedoic acid with ezetimibe used for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or

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established ASCVD who require additional LDL-cholesterol lowering after maximally tolerated statin therapy.

▶ Nicotinic Acid (Prescription Products):

Ex: Niacin(vitamin B3)

S.E: flushing, itching, gastric distress, headache, hepatotoxicity, hyperglycemia, and hyperuricemia

- Niacin used at doses higher than those used as a nutritional supplement

MOA: Niacin inhibits FA release from adipose tissue and FA and triglyceride production in liver cells.

-results in a reduction in the number of VLDL particles secreted, which leads to an overall reduction in LDL cholesterol.

- it is indicated for patients with elevated triglycerides, low HDL cholesterol, and elevated LDL cholesterol.

-the formulations are available: immediaterelease (IR), sustained-release (SR), and extended-release (ER).

-Limitations of niacin IR and SR are flushing and hepatotoxicity, respectively.

-Niacin IR not regulated by the FDA.

-Niacin ER (Niaspan) was developed as a once-daily formulation to be taken **at bedtime**, with the goal of reducing the incidence of flushing without increasing the the risk of hepatotoxicity

-Niaspan is the only long-acting niacin product approved by the FDA for dyslipidemia.

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-Niacin use is limited by cutaneous reactions such as flushing and pruritus of the face and body→ كيف احلها ؟؟

1-use of aspirin or a nonsteroidal anti-inflammatory drug (NSAID) 30 minutes prior to taking niacin can help alleviate these reactionss because they are mediated by an increase in prostaglandin D2

2-taking niacin with food

3-avoiding hot liquids or alcohol at the time niacin is taken

4-slow titration of the niacin dose to minimize and/or prevent flushing (eg, 500 mg/day to 1000 mg/day over 8 weeks).

-In general, niacin reduces LDL cholesterol from 5% to 25%, reduces triglycerides by 11% to 60%, and increases HDL cholesterol by 14% to 39%

-Niacin should be instituted at the lowest dose and gradually titrated to a maximum dose of **2 g** daily for ER and SR products

and no more than **6 g** daily for IR products

-niacin products labeled as "no flush" do not contain nicotinic acid and therefore have no therapeutic role in the treatment of lipid disorders.

-The time until maximum effect on lipids for niacins is generally 3 to 5 weeks.

▶ Fibrates:

Ex : Fenofibrate, Gemfibrozil

The predominant effects of fibrates are a decrease in triglyceride levels by 20% to 60% and an increase in HDL cholesterol levels by 9% to 30% .

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-**Fibrates are the most effective triglyceride-lowering drugs and are used primarily in patients with elevated triglycerides and low HDL cholesterol.**

S.E: dyspepsia, abdominal pain, diarrhea, flatulence, rash, muscle pain, and fatigue

-If a fibrate is used with a statin→ fenofibrate is preferred because it appears to inhibit the glucuronidation of the statins less than gemfibrozil.

-A CK level should be checked before therapy is started and if symptoms occur

-Fibrates should be avoided with severe renal dysfunction (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m2) (Baseline renal function should be assessed), وبرضو باثرو عالكبد

-Fibrates increase cholesterol in the bile and have caused gallbladder and bile duct disorders, such as **cholelithiasis and cholecystitis**

-Unlike niacin, these agents do not increase glucose or uric acid levels

-Fibrates are contraindicated in patients with gallbladder disease, liver dysfunction, or severe kidney dysfunction

-Risk of bleeding is increased in patients taking both a fibrate and warfarin(espically : gemfibrozil+warfarin→ increase INR) يلي هو تميع الدم

-The time until maximum effect on lipids is generally 2 weeks for fenofibrate and 3 to 4 weeks for gemfibrozil.

▶ Omega-3 Fatty Acids:

Ex: Omega-3 ethyl esters, Icosapent ethyl

S.E: associated with long-chain OM3FA are dyspepsia and eructation

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-Long-chain OM3FA may be useful for patients with high triglycerides despite diet and weight loss, alcohol restriction, and fibrate therapy

-EPA and DHA both have the ability to lower triglycerides, but DHA also leads to increases in LDL cholesterol whereas EPA does not increase

-Long-chain OM3FA have other cardiac effects such as reduced platelet aggregation and antiarrhythmic properties.

- EPA and DHA both have the ability to lower triglycerides, but DHA also leads to increases in LDL cholesterol whereas EPA does not increase.

-Prescription-grade long-chain OM3FA ethyl esters and free FA formulations are FDA approved at a dose of 2 to 4 g daily for the treatment of elevated triglycerides (≥ 500 mg/dL [5.65 mmol/L]).

-the FDA approved **icosapent ethyl** as adjunct to:

maximally tolerated statin therapy→ to reduce the risk of MI, stroke, coronary revascularization, and unstable angina requiring hospitalization in **adult patients with triglyceride levels greater than or equal to 150 mg/dL (1.70 mmol/L) and established ASCVD or DM and two or more additional risk factors for CV disease** (ie, male > 55 years of age or female > 65 years of age, tobacco smoker, hypertension, low HDL cholesterol, hs-CRP > 3 mg/L, renal dysfunction, retinopathy, albuminuria, ABI < 0.9).

هاد الدوا بينضاف مع الستاتين كعامل مساعد وليس علاج دوائي للناس يلي لسا مرتفع عندها الترايجلسرايد وعندها مشاكل قلبية او عندها سكريو حققت شطرين من الريسك يلي بزيدو مشاكل القلب .

-excessive amounts of long-chain OM3FA (eg, > 3 g daily) may lead to bleeding خاصة لو المريض بياخدها مع ادوية مضادة للتخثر

▶ Microsomal Triglyceride Transport Inhibitors

Ex: Lomitapide

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MOA: inhibiting the normal transfer of triglycerides to Apo B in the lumen of the endoplasmic reticulum and preventing the assembly of Apo B–containing lipoproteins in enterocytes and hepatocytes.

ونحن عارفين انه الابو-ب , بيدخل بتصنيع الليبوبروتين وبكون على سطحهم الخارجي , فلما امنع المكونات ببطل عندي تصنيع

S.E: GI side effect, elevation in liver enzymes and hepatic fat

- FDA approved for the management of patients with homozygous FH

Management of gastrointestinal side effects:

1-strict adherence to a low-fat diet (< 20% of total calories from fat)

2-gradual dose escalation

-Lomitapide is classified as pregnancy category X. يعني مممنووووع ينعطى

▶ Antisense Oligonucleotide Inhibitor of Apo B-100 Synthesis:

Ex: Mipomersen

-is a once-weekly subcutaneous injectable antisense inhibitor of Apo B synthesis

S.E: Injection site reactions, flu-like symptoms, hepatic fat, and liver enzyme elevations(hepatotoxicity)

-Mipomersen is not a substrate for CYP metabolism and is metabolized by endonucleases and exonucleases→ so that they has minimal clinically relevant drug–drug interactions.

-Mipomersen is pregnancy category B.

▶ Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

Ex: Alirocumab and evolocumab

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Pcsk9 bind with ldl receptor (it is doing degradation of these receptor) so that when the level of the receptor decrease لانها تكسرت→ the level of LDL increase وبقلل وبزيد عددهم المستقبلات تكسير عملية وبثبط بروح انا لهيك اتركيز الldl

-Both medications are FDA approved for heterozygous FH or ASCVD as an adjunct to diet and maximally tolerated statin therapy, when additional LDL lowering is required.

-Evolocumab is also indicated as an adjunct in homozygous FH.

-PCSK9 inhibitors as nonstatin therapy that is recommended to be added to maximum tolerated statin therapy in the very-high-risk ASCVD population

-The 2018 AHA/ACC guidelines additionally recommend adding ezetimibe to maximum tolerated statin therapy prior to adding PCSK9 inhibitors as a more cost-effective approach

Combination Pharmacotherapy:

-patients with concomitant elevations in triglycerides may need combination drug therapy to reach their non-HDL cholesterol goal.

-Combination drug therapy is an effective means to achieve greater reductions in non-HDL and LDL cholesterol (statin plus ezetimibe or PCSK9 inhibitor) as well as lowering serum triglycerides (statin plus long-chain OM3FA or fibrate).

▶ Combination Therapy for Elevated LDL Cholesterol

الناس يلي اخدو ستاتين لحاالله وما تحسنو ولا وصلو للجول تبعي اوما قدرو يتحملو الستاتين بهالحالة منعطي كومبينيشن منضيف دوا فيرست لاين انه اضيفه وفي ادوية سكند لاين انه اضيفها

-First-line add-on therapies include ezetimibe or PCSK9 inhibitors

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-Second-line add-on therapies include BAS.

-Bempedoic acid is not mentioned in the guidelines since it was just recently FDA approved

-Some patients, in particular those with genetic forms of hypercholesterolemia such as FH require three or more drugs to manage their disorder.

-The time until maximum effect on lipids for the combinations of statins plus ezetimibe, PCSK9 inhibitors, BAS, or bempedoic acid is generally 4 weeks

-It is recommended that patients with FH obtain a minimum of greater than or equal to 50% reduction in LDL cholesterol

▶ Combination Therapy for Elevated Cholesterol and Triglyceridemia with or without Low HDL Cholesterol

-Fibrates are the most effective triglyceride-lowering agents and also raise HDL cholesterol levels

-gemfibrozil, and a statin has been found to increase the risk for myopathy. لهيك ما بنعطو سوا

- adding fenofibrate to simvastatin therapy has a good benefits → in patients with triglycerides greater than or equal to 204 mg/dL (2.31 mmol/L) and HDL cholesterol less than or equal to 34 mg/dL (0.88 mmol/L).

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